Original Article

Low Intensity Statin for Primary Prevention of Non-Fatal MI and Non-Fatal Stroke in Type 2 Diabetes

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Objective: To compare the efficacy of low intensity statin (simvastatin 10 mg) versus moderate and high intensity statins for primary prevention of non-fatal myocardial infarction and non-fatal stroke in type 2 DM patients.

Materials and Methods: A retrospective cohort study was conducted on type 2 DM patients without prior history of atherosclerotic cardiovascular disease [ASCVD] who attended the endocrine clinic, Faculty of Medicine Vajira Hospital between 1 January 2006 and 30 June 2016, and received statins for primary prevention of ASCVD. Data on cardiovascular events, including non-fatal MI and non-fatal stroke were collected. The association of intensity of statin with cardiovascular events was analyzed with Cox hazard model.

Results: Of the 1,100 type 2 DM patients without prior ASCVD, 446 patients (40.5%) received simvastatin 10 mg and 654 patients (59.5%) received other statins. Patients in the simvastatin 10 mg group had significant lower body mass index, cholesterol, triglyceride and LDL-c level at baseline, also had significant lower composite non-fatal MI and non-fatal stroke than other statins group (HR = 0.479, 95% CI 0.31 to 0.74, p = 0.001]. This was mainly contributed to lower non-fatal MI in the simvastatin 10 mg group (HR = 0.357, 95% CI 0.20 to 0.64, p = 0.001).

Conclusion: Low intensity statin may be sufficient for primary prevention of cardiovascular events in very low risk type 2 DM patients.

Keywords: Low intensity statin, Non-fatal MI, Non-fatal stroke, Primary prevention

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Atherosclerotic cardiovascular disease [ASCVD] is the leading cause of morbidity and mortality for individuals complicated with diabetes mellitus [DM] and is the largest contributor to the direct and indirect cost of diabetes. Patients with type 2 DM have an increase in the prevalence of lipid abnormalities, contributing to their increased risk of ASCVD. Numerous studies have shown the efficacy of statin in primary and secondary cardiovascular disease prevention[1,2]. Trials in patients with DM[3,4] and subgroup analysis of patients with DM in larger trials[5-9] showed markedly primary and secondary prevention of ASCVD. Meta-analysis[10] including data from over 18,000 patients with DM demonstrated 13% reduction in vascular mortality for each mmol/L (39 mg/dL) reduction in LDL cholesterol. Absolute reductions in ASCVD outcomes are greatest in people with high baseline ASCVD risk, but overall benefits of statin therapy in people with DM at moderate or even low risk for ASCVD are convincing[11,12].

Most trials of statin and ASCVD outcomes compared specific dose of statins against placebo or other statins rather than aiming for specific LDL cholesterol goal, suggesting that the initiation and intensification of statin therapy are based on risk profile[13]. Consequently, most of clinical practice guidelines suggest that the intensification of statin treatment is based on individual patient risk. The American diabetes association [ADA] recommends moderate intensity statin for the primary prevention of ASCVD. However, the number of studies of low

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intensity statin for primary prevention of ASCVD is limited. We conducted a retrospective cohort study to compare low intensity statin (simvastatin 10 mg) with other statins for the primary prevention of non-fatal MI and non-fatal stroke in type 2 DM patients.

Materials and Methods

Study population

This was retrospective cohort study of type 2 DM patients who were treated at the endocrine clinic of Faculty of Medicine Vajira Hospital between 1 January 2016 and 30 June 2016. Inclusion criteria were patients who were diagnosed with DM after 30 years, had no previous atherosclerotic cardiovascular disease, and received statin for primary prevention of ASCVD for more than 6 months. Patients who received other lipid lowering agents were excluded. Medical charts of the patients and electronic database were retrospectively reviewed to search for documented cardiovascular event (non-fatal myocardial infarction and non-fatal stroke).

Data collection

Sociodermographic variables included age, gender, education attainment, occupation. Clinical characteristics included duration of diabetes, exercise behavior, smoking/alcohol drinking status, baseline weight, height, body mass index, waist circumference, blood pressure. HbA1c, serum Cr and estimated glomerular filtration rate [eGFR], UACR, lipid profile (total cholesterol, Triglyceride, HDL-c, calculated LDL-c) were obtained at baseline. Data of chronic medication exposures included antiplatelet, lipid lowering agents and antihypertensive drugs. Microvascular complication (diabetes nephropathy, retinopathy, neuropathy) at baseline were also recorded.

Non-fatal myocardial infarction

Non-fatal myocardial infarction included unstable angina, non ST elevated [NSTEMI], ST elevated myocardial infarction [STEMI] and CAD related interventions (coronary artery bypass surgery, percutaneous transluminal coronary angioplasty). Individual who developed cardiovascular death were excluded because OPD records and electronic database were destroyed after patients died for 5 years. Date, clinical presentation, diagnostic method and treatment result were recorded. Diagnosis of myocardial infarction was determined by cardiologist.

Non-fatal stroke

Non-fatal stroke included acute ischemic stroke, hemorrhagic stroke and transient ischemic attack. We excluded patients with fatal stroke due to OPD records and electronic database were destroy after patients died for 5 years. Date, clinical presentation, diagnostic method and treatment result were recorded. Stroke diagnosis was verified by neurologist

Statistical analysis

We assessed the association of intensity of statin (simvastatin 10 mg with other statins) and cardiovascular events with Cox hazard model. Differences of demographic variables and baseline characteristic between groups were compared using t-test and Chi-square test. The *p*-value for determine statistical significant was <0.05. Statistical analyses were performed by SPSS statistical analysis program for windows version 22.0 (IBM Corp, Armonk, NY).

Results

A total of 1581 patients were followed at the endocrine clinic, Faculty of Medicine Vajira Hospital between 1 January 2016 and 30 June 2016. After excluding patients who were diagnosed with diabetes before aged 30 and patient with type 1 DM, not receive statin, and those receiving other lipid lowering agents and had prior cardiovascular disease, there were 1,100 DM patients remained for analysis (Figure 1): 446 patients (40.5%) received simvastatin 10 mg and 654

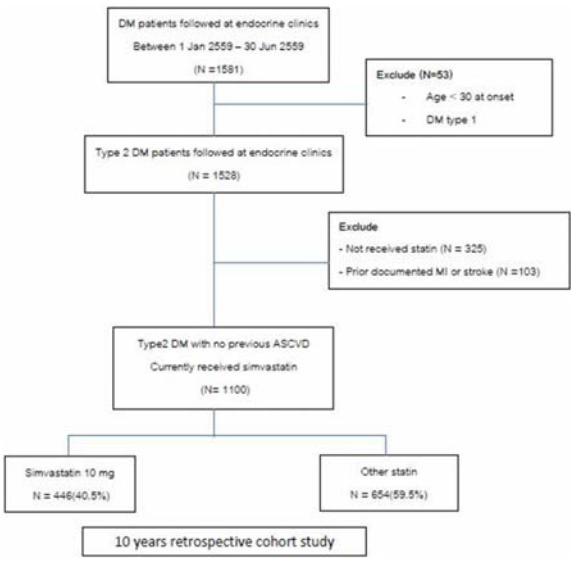

Figure 1. Enrollment and outcomes.

(59.5%) received other statins. Patients in simvastatin 10 mg had significant lower baseline BMI, Cholesterol, Triglyceride, LDL-c than other statin group. Lower proportion of simvastatin 10 mg group received ACEi/ARB. A total of 109 (9.9%) patients developed cardiovascular event between study period. Seventy two (6.5%) patients had non-fatal MI and 37 (3.4%) patients had non-fatal stroke (Table 1).

Cardiovascular events

The primary outcome (composite of non-fatal MI and non-fatal stroke) occurred in a significantly lower percentage of patients in the simvastatin 10 mg group (26 of 446 or 5.8%) than in the other statins group (83 of 654 or 12.7%) (hazard ratio [HR], 0.479, 95% CI (0.31 to 0.74), $p = 0.001$) (Figure 2A). For the secondary outcome, simvastatin 10 mg resulted in a significant lower incident of non-fatal myocardial infarction (14 of 446 or 3.1%) than other statins group (58 of 654 or 8.9%) (HR = 0.357, 95% CI (0.20 to 0.64), $p = 0.001$) (Figure 2B). There were no significant differences between the two groups in terms of the occurrence of non-fatal stroke, (12 of 446 or 2.7%) in simvastatin 10 mg group and (25 of 654 or 3.8%) in other statins group

Table 1. Baseline characteristics of the study population

	Simvastatin 10 mg (n = 446)	Other statin (n = 654)	*p*-value
Age Y	66.8±10.8	66.3±11.1	0.415
Male	133 (29.8%)	232 (35.5%)	0.051
Duration 0f DM	15.8±7.8	15.4±8.0	0.491
Smoking/Alcohol	62 (13.9%)	86 (13.1%)	0.716
Retinopathy	43 (9.6%)	63 (9.6%)	0.996
Neuropathy	37 (8.3%)	54 (8.3%)	0.982
ESRD	5 (1.1%)	11 (1.7%)	0.446
BMI	26.4±4.7	27.4±5.0	0.001
BP			
SBP	136±19.5	137±18.9	0.355
DBP	76.4±17.4	77±11.3	0.345
A1C	8.2±1.9	8.3±1.9	0.244
Cr	1.04±0.55	1.12±0.85	0.06
eGFR	76.6±25.2	73.8±26.3	0.78
UACR			
<30	235	316	
30-229	137	227	0.167
≥300	46	90	0.088
NA	28	21	
Lipid			
Cholesterol	180.80±37.4	187.90±42.2	0.004
Triglyceride	143.05±86.1	158.29±106.5	0.012
HDL-c	46.78±12.3	46.0±12.8	0.308
LDL-c	105.72±32.2	110.3±35.8	0.029
Medication			
Antiplatelet	198	326	0.075
ASA	195	318	0.11
Plavix	3	8	0.37
ACEi/ARB	357 (80.0%)	556 (85.0%)	0.031
CV events			
MI+Stroke	26	83	
Non-fatal MI	14 (3.1%)	58 (8.9%)	
Non-fatal Stroke	12 (2.7%)	25 (3.8%)	

ESRD = end stage renal disease; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic BP; UACR = urine albumin/creatinine ratio; MI = myocardial infarction

(HR = 1.297, 95% CI (0.67 to 2.51), $p = 0.441$) (Figure 2C).

Discussion

Most clinical practice guidelines recommended moderate and high intensity statin for primary prevention of ASCVD in type 2 diabetes patients. This is 10 years retrospective cohort study, most of the patients received treatment before recommendation of new clinical practice guideline were published and intensification of statin base on LDL-c target.

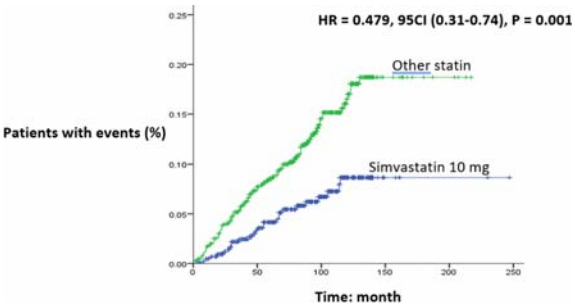

Figure 2A. Combined non-fatal MI and non-fatal stroke.

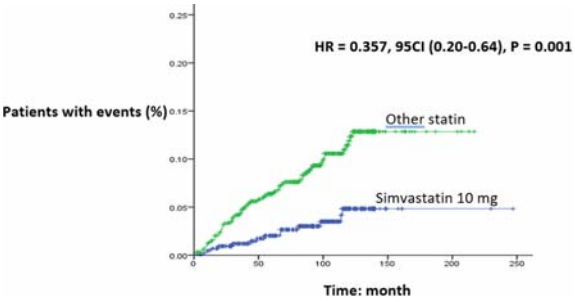

Figure 2B. Non-fatal MI.

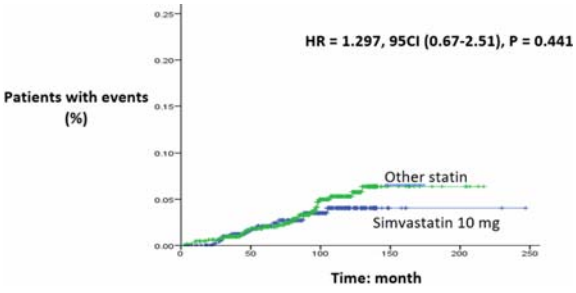

Figure 2C. Non-fatal stroke.

Consequently, many physicians prescribed low intensity statin to their patients that have mild elevated and easily to control LDL-c level.

In the present study, patients in simvastatin 10 mg group had significant lower composite non-fatal MI and non-fatal stroke than other statins group. This was primarily to significant lower non-fatal MI in simvastatin 10 mg group but not significant between group differences in the occurrence of non-fatal stroke. Patients in the simvastatin 10 mg group tends to have lower baseline cardiovascular risk due to significant lower BMI, lipid profile (cholesterol, triglyceride, LDL cholesterol) and this may resulting in lower incident of composite non-fatal MI and non-fatal stroke.

Lower baseline cholesterol and LDL cholesterol may made physicians to prescribe low intensity statin to their patients. However, when adjusted for BMI, baseline cholesterol, LDL cholesterol, simvastatin 10 mg group still had significant lower composite non-fatal MI and non-fatal stroke than other statins group.The results in this study imply that low intensity statn may sufficient for control lipid level and for primary prevention of ASCVD in patients with low baseline cardioveascular risk and minimally elevated LDL cholesterol level.

Limitation in this study is due to lack of cardiovascular death data and some informations in OPD records maybe error or missing.

Conclusion

Low intensity statin (simvastatin 10 mg) may be sufficient for primary prevention of CV event in very low risk type 2 DM patient that have easily to control lipid level and other risk factors.

What is already known on this topic?

Statin has shown benefit in primary and secondary cardiovascular disease prevention. Most of clinical practice guideline recommended moderate intensity statin for primary prevention of ASCVD in patients with type 2 diabetes mellitus. However, many patients in clinical practice received low intensity statins which is only dose of statin that patients can tolerate.

What this study adds?

This study confirmed the benefit of low intensity statin for primary prevention of ASCVD in type 2 DM patients. Also provided clinicians of evidence that low intensity statin still has benefit in clinical practice.

Potential conflicts of interest

The authors declare no conflict of interest.

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