Chapter 10

Statins in Type 2 Diabetes

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1. Introduction

Cardiovascular disease (CVD) is one of the foremost causes of mortality and is a major contributor to morbidity for individuals with diabetes. Lipids abnormalities play an important role in raising the cardiovascular risk in diabetic and obese individuals. The main components of dyslipidemia in diabetes and metabolic syndrome is documented as small, dense low-density lipoprotein (LDL-cholesterol), the elevation in remnant triglyceride-rich lipoprotein particles, and the low high-density lipoprotein (HDL-cholesterol), which have very powerful atherogenic components.

Diabetes and chronic diseases such as chronic kidney diseases (CKD) were assessed as high-risk for cardiovascular risks by JNC-7, JSH-2009, the Adult Treatment Program III (ATP III)., therefore those conditions require more aggressive control of hypertension and dyslipidemia. [1, 2, 3, 4]. The American Heart Association (AHA) and the American College of Cardiology (ACC) recommended the following four groups of patients should be treated by statins; (1) patients with cardiovascular disease including angina, a previous heart attack or stroke, or other related condition; (2) patients with an LDL cholesterol ≥190 mg/dL; (3) patients with type 2 diabetes aged between 40 and 75 years. They reported that (4) patients with an estimated 10-year risk of cardiovascular diseases including a heart attack or stroke or developing other form of cardiovascular disease of ≥7.5% aged between 40 and 75 years. In addition, both Adult Treatment Program (ATP III) [3] and the American Diabetes Association (ADA) [4] guidelines have identified low-density lipoprotein cholesterol and the first priority of lipid lowering. There is strong evidence from landmark secondary prevention studies, that LDL cholesterol lowering in patients with diabetes leads to significant clinical benefits. Therefore, the benefit of statins on type 2 diabetes has been confirmed. [5]

Assellberg *et al.* [6] found 4 polymorphisms for HDL-cholesterol, 6 polymorphisms of LDL-cholesterol, 10 for total cholesterol, and 4 polymorphisms for triglycerides might be responsible

for these lipids' parameters phenotypes in the investigation using 2,000 genes.Genome-wide association studies (GWASs) have shown strong relationships between genetric polymorphisms and lipids levels. Dyslipidemia may have, at least partly, determined genetic backgrounds, and understanding the heritability of dyslipidemia may help to control dyslipidemia.

Dyslipidemia is known as one of the important causes for the atherogenic changes in cardiovascular system, and results in very severe cardiovascular risk. Therefore, diabetes patients with dyslipidemia have much higher prevalence of mortality and morbidity of cardiovascular risks compared to diabetes patients without dyslipidemia. However, there have been a lot of discussions, especially required statins on type 2 diabetes, because statins increase the risk of new-onset type 2 diabetes mellitus [7-9]. Very recent genetic meta-analysis suggested that the increased risk of type 2 diabetes noted with statins is at least partially explained by 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase or HMGCR) inhibition [10].

The statins work in the liver to prevent the formation of cholesterol. This class of drugs are most effective at lowering the LDL- cholesterol, but also have modest effects on lowering triglycerides and raising HDL- cholesterol. There are several large cohort studies investigating the effects of statins on cardiovascular risks such as the Scandinavian Simvastatin Survival Study (4S) [11] and the Cholesterol and Recurrent Events (CARE) [12, 13] trial, however, the results are discordant. Some studies showed the drugs to reduce a patient's risk of cardiac events and stroke, outside of their ability to lower cholesterol levels. On the other hand, the statins are known as their side effects including elevation in glucose levels, which is well documented as one of the risk factors for ischemic heart diseases. A number of investigations have shown that people on a high-dose regimen of the cholesterol drug atorvastatin and other cholesterol-lowering drugs may have a slightly increased risk of developing type 2 diabetes, particularly if they have several of the classic diabetes risk factors. Therefore, the American Heart Association (AHA) /The American College of Cardiology (ACC) stated separately the guideline on dyslipidemia in 2013 [14].

This chapter will review *i)* at first, dyslipidemia as a risk factor for cardiovascular diseases, and then *ii)* the benefits and demerits for dyslipidemia treatments in type 2 diabetes using statins based on the data in several large cohort studies. *iii)* Furthermore, the discrepancy, statins can improve dyslipidemia but cannot prevent the new onset of type 2 diabetes, will be discussed.

2. Statins in type 2 diabetes—Friends or Foe?

2.1. Dyslipidemia is one of the criteria of metabolic syndrome, pre-stage of type 2 diabetes

Prevalence of metabolic syndrome has been increasing with prevalence of obesity. The pathophysiology of metabolic syndrome is very complicated, but has been partially understood. It has been well documented metabolic syndrome is an important risk factor for cardiovascular diseases, especially heart diseases including heart failure and ischemic heart disease. Some studies have shown the prevalence of metabolic syndrome in the USA to be an estimated 34% of the adult population [15], and the prevalence increases with age. In addition, weight gain is associated with metabolic syndrome. Central obesity is the most important

confounder of metabolic syndrome, therefore, waist circumference may represent the existence of metabolic syndrome (Table 1). Another key confounder of metabolic syndrome is insulin resistance [20, 21]. Hypertensive patients, even they are nonobese, show high prevalence of insulin resistance, and metabolic syndrome coexists. Usually, people with metabolic syndrome has higher risk of developing cardiac events by twice and diabetes by 5 times compared to individuals who do not have metabolic syndrome. Therefore, hypertensive patients, even not obese, with metabolic syndrome have very high risks of cardiac events and diabetes.

	WHO (16)	**EGIR** (17, 18)	**NCEP AT III (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults)** (3)	**American Heart Association Updated NCEP III** (19)
Insulin resistance	Top 25% of population Distribution	Top 25% of population distribution	Not considered	Not considered
Hyperinsulinemia	Not considered	Top 25% of population	Not considered	Not considered
Fasting glucose (mmol/L)	impaired fasting glucose, or impaired glucose tolerance or diabetes	>6.1, but not diabetic	≥6.1	≥5.6 (100 mg/dL) or medications for hyperglycemia
Hypertension (mmHg)	≥160/≥ 90	≥140/≥ 90 or on medications for hypertension	≥130/85	≥130/85 or medications for hypertension
Central obesity	waist/hip ratio >0.9 (men), >0.85 (women) and/or BMI≥30kg/m^2			
Waist circumference (cm)	Not considered	≥94 (men), ≥ 80 (women)	>102 (men), >88 (women)	≥102 (men), ≥88 (women)
HDL-cholesterol (mmol/L)	<1.0 or medications for dyslipidemia	<1.0 or medications for dyslipidemia	<1.07 (40 mg/dL, men), <1.25 (50 mg/dL , women)	<1.07 (40 mg/dL, men) 25 (50 mg/dL, women)
Triglyceride (mmol/L)	<1.0 or medications for Dyslipidemia	>2.0 or medications for dyslipidemia	≥1.695 (150 mg/dL)	≥1.695 (150 mg/dL)
Micro-albuminemia	Present	Not considered	Not considered	Not considered
Criteria	1 of the first two + 2 of other features	2 of other features	3 of above	3 of above

BMI, body mass index; EGIR, European Group of the study of Insulin Resistance; NCEP ATPIII, 3rd Recommendations of the Adult Treatment Panel of the National Cholesterol Education Program; HDL-cholesterol, high-density lipoprotein cholesterol. Values in NECP definition and American Heart Association/Updated NCEP are approximations of values in mg/dL.

Table 1. Criteria for Metabolic Syndrome including Insulin Resistance (11)

In addition, many epidemiological and clinical studies have shown that insulin resistance may lead to dyslipidemia; Dyslipidemia, especially low HDL-cholesterol and high triglycerides are also important criteria with high glucose levels for the metabolic syndrome (Table 1). Carg [22] hypothesized approximately 20 years ago that insulin resistance might cause dyslipidemia in metabolic syndrome. Ruotolo and Howard [23] suggested that hyperinsulinemia as a compensatory mechanisms of insulin resistance leaded to, at first, very low-density of lipoprotein (VLDL) cholesterol overproduction, then the decreased clearance of fasting and postprandial triglyceride rich lipoproteins (TRLs), and the decreased production of HDL particles [23]. In addition, they suggested that increases in TRLs play major role in metabolic syndrome, and elevated VLDL-cholesterol and decreased HDL-cholesterol may be consequence of TRLs elevation. Very recently, the Framingham study [24] supported the close relationship between dyslipidemia and insulin resistance for the onset of coronary heart disease. The incidence of coronary heart disease risk associated with HDL-cholesterol or triglycerides were significantly increased only in the presence of insulin resistance.

2.2. Dyslipidemia is an atherogenic factor

It is well established that elevation of serum LDL is a major cause of atherosclerosis and coronary heart disease (CHD) [25-29]. Many epidemiological studies have shown that elevated LDL cholesterol level is strongly related to future cardiac events [30, 31]. Therefore, LDL-cholesterol can be used as an important predictor for the future cardiac events in cardiac risk assessments (*i.e.* the Framingham Risk Score) [30, 31]. However, it is also known that other serum lipoproteins, such as triglyceride-rich lipoproteins (TRLs), very low-density lipoproteins (VLDL), chylomicrons, and HDL-cholesterol, are involved. In atherogenic dyslipidemia, the pattern of lipoprotein abnormalities or atherogenic lipoprotein phenotype includes elevations of VLDL levels, increased small LDL particles, and low HDL-cholesterol [32, 33]. The abnormalities usually coexist because they have a common metabolic basis. Grundy summarized and figured the relationship insulin resistance, dyslipidemia and coronary heart disease [34]. Besides the multiple mechanisms for atherogenesis accompanying the lipid triad, atherogenic dyslipidemia commonly is associated with several non-lipid risk factors as part of metabolic syndrome (insulin resistance) [35]. In addition, the prothrombotic state may be accompanied by several abnormalities in the coagulation system in metabolic syndrome; most notable are elevations in fibrinogen and plasminogen activator inhibitor-1 (PAI-1). These phenomena might be related to the onset and development of atherogenic damage in vessels

2.3. Statins can improve dyslipidemia in type 2 diabetes, and result in the prevention for coronary heart diseases or other cardiovascular events.

A number of large cohort clinical studies on the efficacy of statins, especially atorvastatin, have been conducted for the primary and secondary prevention of cardiovascular events in adults with, or at risk of, coronary heart disease (CHD). [36, 37] In primary prevention, CARDS (Collaborative Atorvastatin Diabetes Study) [38] showed that atorvastatin 10 mg/day significantly reduced cardiovascular events compared to placebo (relative risk of the composite primary endpoint; acute CHD events, coronary revascularisation, or stroke) by 37% ($p = 0.001$).

The decrease of cardiovascular events in CARDS study with atorvastatin was similar to those in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) with atorvastatin [39, 40] and HPS (Heart Protection Study) with simvastatin [41]. However, lipids lowering effects of atorvastatin was observed to be faster compared to simvastatin, 6 months with atorvastatin observed in CARDS [38] versus 15-18 months in simvastatin observed in HPS [41]. The ASCOT-LLA trial [39] conducted in 2,226 hypertensive diabetic patients without previous cardiovascular disease, showed that atorvastatin could decrease the relative risk on primary coronary heart diseases (CHD) by 36% (p=0.0005), and all cardiovascular diseases (CVD) risk by 25% (p = 0.038) compared to placebo. The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) [42, 43] and TNT (Treating to New Targets) trials [44, 45] demonstrate that both low (10 mg/day) and high (80 mg/day) doses of atorvastatin reduced the risk of non-fatal myocardial infarction by 17-22% ($p < 0.02$). [42-45]

Sub-studies of the GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation) [45-48], TNT (Treating to New Targets) [43, 49-51] and PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) [52-54] trials showed similar results of atorvastatin reduced cardiac events but not only patients without diabetes but also in those with diabetes. Those studies included 15-25% of patients with diabetes.

In the GREACE sub-study, which compared to physicians'standard care [47], atorvastatin significantly reduced the relative risk of total mortality and cardiac moratility and morbidity (coronary mortality, coronary morbidity, and stroke). Furthermore, atorvastatin improved renal function [47] and liver function [46]. Of interest, patients with non-alcoholic fatty liver disease, statins (atorvastatin 24 mg/day) improved liver function, although liver injury was worsen in others without statin treatment for dyslipidemia. This study demonstrated that statin treatment is safe for mild-to-moderate liver injury caused by non-fatty liver disease, and can improve liver injury and reduce cardiovascular morbidity. In addition, statins treatment has benefits for all age groups including old patients. In the older patients, intensive lipids lowering treatments are more effective to reduce cardiovascular risks compared to younger patients when compared to usual lipids lowering treatment. The GREACE study demonstrated that one should not deprive older patients of CVD prevention treatment and lipid target achievement. [48]

Similarly, TNT (Treating to New Targets) trials [49, 50] demonstrate the preventive efficacy of atorvastatin on the reductions of cardiac events in patients with stable CHD. In the TNT sub-study [51] including a total of 9,251 coronary heart disease patients with low-density lipoprotein cholesterol, higher dose of atorvastatin (80 mg/day) over 4.9 years was more effective on the prevention on major cardiovascular events (n=729) such as coronary death, non-fatal myocardial infarction, cardiac arrest, or stroke regardless of fatal or non-fatal, compared to lower dose (10 mg/day). [52] In sub-analysis of TNT trial conducted in 5,584 CHD patients with metabolic syndrome, higher dose of atorvastatin (80mg/day) reduced the major cardiovascular and cerevrovascular events by 29%. In addition, this sub-study also demonstrated that CHD patients with metabolic syndrome had a 44% greater level of absolute cardiovascular risk compared to those without metabolic syndrome, indicating the clinical feasibility of administering intensive lipid-lowering therapy to CHD patients with metabolic syndrome

[53]. In addition, the other sub-analysis [43] demonstrated even in treatment resistant hypertensive patients, who were at high risk of cardiac events, intensive lipid lowering with atorvastatin 80 mg is associated with a significant reduction in cardiovascular events.

In the PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) sub-study [54, 55], a significantly lower incidence of acute cardiac events was reported in patients with atorvastatin compared to pravastatin (21.1% vs. 26.6%; $p = 0.03$). Therefore, an absolute risk reduction of 5.5% was associated with atorvastatin therapy [54-56]. Similarly, the IDEAL trial (the Incremental Decrease in End Points through Aggressive Lipid Lowering trial) [57] compared the effects on cardiovascular risks between atorvastatin 80 mg daily versus simvastatin 20-40 mg daily in post-myocardial infarction patients. The IDEAL trial had smaller statistical power due to the smaller number of patients compared to the PROVE-IT study, but longer follow-up (5 years vs. 2 years). Interestingly, decreases in the relative risk of cardiovascular events at 5 years in group with simvastatin was similar to that in the 2-year follow-up with atorvastatin group, and the decreases in the cardiovascular risk maintained consistently from 2 years to 5 years in atorvastatin group. The 2 treatment regimens (atorvastatin versus simvastatin) were well tolerated. These results indicated that patients with recent myocardial infarction should be on intensive statin therapy with atorvastatin and maintain the high dose of atorvastatin as long as possible, over 2 years.

ASPEN (Atorvastatin Study for Prevention of coronary heart disease Endpoints in Non-insulin-dependent diabetes mellitus) [58] in 2,410 type 2 diabetic patients demonstrated that a 29% lower low-density lipoprotein-cholesterol level was seen with atorvastatin than placebo at endpoint ($p < 0.0001$) over a 4-year period. In sub-analysis in the 505 subjects with prior myocardial infarction or interventional procedure, atorvastatin did not reduce relative risk of a primary end-point (cardiovascular mortality, non-fatal major cardiovascular event, stroke, and unstable angina pectoris, fatal or non-fatal myocardial infaction). Therefore, ASPEN trial failed to confirm the benefit of atorvastatin on cardiocvascular risk in type 2 diabetes [58].

The ALLIANCE (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events) [59-61] and GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation) [62, 63] trials demonstrated the benefits of treatment with atorvastatin for dyslipidemia compared to usual care with generic statins as the real practical clinic (*i.e.* simvastatin) in patients with stable CHD. Atorvastatin reduced the risk of non-fatal myocardial infarction by 47-59% ($p < 0.0002$) compared to usual dyslipidemia therapy with generic statins as a usual community practice in 2008. The MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) [64, 65], PROVE-IT [54] and IDEAL-ACS (Acute Coronary Syndromes) [57] studies also recommend the benefits of high-dosage atorvastatin therapy started from early phase after the onset of acute coronary syndrome such as within 24-96 hours observed in the MIRACL trial. When compared to placebo, all statins including pravastatin and simvastatin, atorvastatin are effective to reduce the risk of death or major cardiovascular events by 16-18% ($p = 0.048$). In patients undergoing revascularization procedures, the AVERT (Atorvastatin VErsus Revascularization Treatment) study [66] revealed that administration of atorvastatin 80 mg/day over 18 months had similar benefits on reducing the ischemic cardiac risk to angioplastity plus usual care in low-risk patients with stable coronary artery disease. Furthermore, Arca [62] reviewed

that the ARMYDA (Atorvastatin for Reduction in MYocardial DAmage during angioplasty) and ARMYDA-3 trials showed atorvastatin's benefits on myocardial infaction patients; Atorvastatin 40 mg/day over 7 days before coronary intervention significantly reduced the risks of myocardial ischemic damage (ARMYDA), post-procedural acute myocardial infarction (ARMYDA) and atrial fibrillation (ARMYDA-3) versus placebo. In addition, it has been observed that post-myocardial infactionm patients without atorvastatin have significantly higher C-reactive protein levels and higher prevalence of the combined incidence of cardiovascular events (death, MI and target segment revascularization during the 6-month follow-up). In addition, the ATTEMP study (Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabetes) [67] showed atorvastatin improved renal function and reduced serum uric acid levels in metabolic syndrome without cardiovascular diseases. These changes were more prominent in stage 3 chronic kidney diseases patients and might have contributed to the reduction in cardiovascular risk and clinical events.

Overall, therefore, the marked efficacy of atorvastatin in the primary and secondary prevention of cardiovascular events were provided in many large cohort trials not only in relative healthy individuals, but also in diabetes or post-myocardial infarction patients, and the effects were stronger than usual statins such as simvastatin. Atorvastatin has in general cardiovascular disease management including improving renal function, and liver injury with non-alcoholic fatty liver, suggests even greater potential clinical utility for the drug in some clinical settings. [37, 66] The results from the meta-analysis using 31 randomized studies compared statins and placebo or other statins showed in patients with CVD, (or at risk of CVD), statin reduced relative risk of all cause mortality, cardiovascular mortality, coronary heart disease mortality and fatal myocardial infarction, but did not reduce the risk of fatal stroke. Statin could not reduce relative risk of morbidity of non-fatal stroke, non-fatal myocardial infarction, transient ischemic attack (TIA), unstable angina, and coronary revascularization.

The differentiations on the clinical efficacy between statins; atorvastatin, fluvastatin, pravastatin and simvastatin, are almost impossible from the previous large clinical studies, however, there is some evidence from direct comparisons between statins to suggest that atorvastatin may be more effective than pravastatin in patients with symptomatic coronary heart diseases, although there is limited evidence for the effectiveness of statins in different subgroups [67].

2.4. Statins may improve renal function

The comparisons analysis related to renal function [43] from clinical trials with data from 149,882 patient-years of follow-up failed to show an association between high-potency statins and risk of acute kidney injury with statins (10,345 patients on atorvastation, 10-80 mg/day) compared with controls (placebo, 8,945 patients with placebo). In addition, there were no differences in effects on renal function between high-dose versus low-dose. This comparison was performed in the 24 placebo-controlled trials including IDEAL [57], TNT [47], CARDS [69, 70], ASPEN (The Atorvastatin Study for Prevention of coronary heart disease Endopoints in Non-diabeties mellitus) [58], SPARCL (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) [43, 71], and other large study using placebo with 10,345 patients with atorvastatin and 8945 patients with placebo. [43]

The TNT trial in 10,001 CHD patients with and without pre-existing chronic kidney diseases demonstrated efficacy of atorvastatin (80 mg/day) on reduction of CHD risk as well as improving renal function in both with and without pre-existing renal injury patients. No difference in the incidence of renal-related serious adverse events were observed at 120 days (0.04% in atorvastatin; 0.10% in placebo, p = 0.162) [50, 51]. Similarly, the use of a high-potency statin regimen did not increase the risk of kidney injury was observed in 2 large randomized trials of statin therapy in patients with acute coronary syndrome; PROVE IT-TIMI 22 [50, 55] (atorvastatin 80 mg/day) including 4,162 patients, and A-to-Z trial (pravastatin 40 mg/day for 1 month + simvastatin 80 mg/day after 1 month) including 4, 497 patients. [72] As mentioned in the previous section, the ATTEMP (Assessing the treatment Effect in Metabolic syndrome without Perceptible diabetes) study [67] showed that multifactorial intervention in patients with metabolic syndrome without established CVD improved renal function and reduced serum uric acid levels. Of importance, these changes were more prominent in stage 3 chronic kidney diseases patients. PROVE-IT-TIMI 22 sub-study [73] used urinary albumin excretion as an index of renal injury, showed no significant change in urinary albumin concentration from enrollment to end of study in either the standard (pravastatin 40 mg/day) or intensive (atorvastatin 80 mg/day) statin therapy groups in an acute coronary syndrome in statin treated patient. [52] Microalbuminuria may reflect traditional cardiovascular risk factor burden and offer little prognostic information independent of those factors. [52]

2.5. Cost-effectiveness

Cost-effectiveness between statins has been compared in several studies such as the Aggressive Lipid-lowering Initiation Abates New Cardiac Events study (ALLIANCE study) [73], and those observations showed the advantage of atorvastatin in high-risk CVD patients [68] and type 2 diabetes patients [74]. Despite the non-adherence levels observed in actual practice, statin treatment is cost-effective for primary prevention in patients newly diagnosed with type 2 diabetes. Because of large differences in cost-effectiveness according to different risk and age groups, the efficiency of the treatment could be increased by targeting patients with relatively higher cardiovascular risk and higher ages [74]. When the efficacy and cost-effectiveness were compared between rosuvastatin, atorvastatin, pravastatin and simvastatin, rosuvastatin therapy in commonly prescribed doses is most effective for improving hypercholesterolemia and most cost effective in diabetic patients with and without metabolic syndrome. [75] The PROVE IT trial [76] demonstrated that atorvastatin 80 mg/day has stronger efficacy on reducing cardiovascular events compared to pravastatin 40 mg/day in patients with acute coronary syndrome. Genetic investigations in PROVE-IT sub-study showed that the prevalence of event reduction was greater in carriers of the Trp719Arg variant in kinesin family member 6 protein (KIF6) than in non-carriers. Parthan *et al.* [76] assessed the cost effectiveness of testing for the KIF6 variant followed by targeted statin therapy (KIF6 Testing) versus not testing patients, and they found that cost-effectiveness is sensitive to the price of generic atorvastatin and the effect on adherence of knowing KIF6 carrier status.

2.6. The JUPITER trial and meta-analyses show statins increase the risk of new onset of type 2 diabetes

Statins are known as well-tolerated and very rare adverse events reported. Side effects of statins are very rare but still exist such as elevations of liver enzymes, muscle aches, and very rarely, rhabdomyolysis [76]. If people have adverse events, discontinuation is primary as usual procedure to resolve these adverse events similarly to other any medications.. Recently, debate has focused on the possible negative long-term effects of statin treatment on cognitive decline, and the incidence of cancer [78]. Some investigators have documented that statins affect the risk of developing cancer, when they are taken at low doses for managing hypercholesterolaemia. There is some possibility of an increased cancer risk in elderly patients associated with hydrophilic statin use. On the other hand, some recent studies have shown the benefits of statins in modifying the prognosis of cancer, and the decreases in the risks of certain cancers, such as gastric, oesophageal, liver, colorectal and advanced/aggressive prostate cancer. In addition, Jukema *et al.* [78] reported that there was no increased risk of cognitive decline or cancer with statin use. However, regarding the relations between statins and cancer, results remain controversial. Further investigations will be necessary to clarify.

Since the report of the new onset of diabetes during rosuvastatin treatment, as an unexpected finding in the JUPITER trial [7], safety concerns on abnormal glucose metabolisms related to statins have emerged in 2012. The possible association of diabetes with statin therapy has been discussed over several years, but statins' effects on reducing of cardiovasculoar risk has been overweighted than the new onset of diabetes or glucose metabolism impairement. In addition, guidelines of the American Diabetes Association [3], American Heart Association [1, 14], and American Copllege of Cardiology [14] have shown the same direction of overweighting on dyslipidemia control. In addition, several studies and meta-analysis data have shown that statin use is related to a small increased risk of type 2 diabetes mellitus. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial [79-81] demonstrated new onset of diabetes, although rosuvastatin reduces cardiovascular events and all-cause mortality and concomitant evidence of moderate chronic kidney diseases. The JUPITER finding on impairement of glucose metabolisms was the first data showing the strong relationship between statins and the new onset of diabetes. The JUPITER trial [78, 80]was conducted in 17,603 men and women without histories of cardiovascular diseases or diabetes with randomized, double blind design to evaluate the efficacy of rosuvastatin 20 mg/day over 5 years. In this trial, the participants who had diabetes risk factor (n=11,508), showed developing diabetes more frequently than those without a diabetic risk factor (n=6,095). In individuals with diabetic risk factors, rosuvastatin decreased the cardiovascular risks such as the primary endpoint by 39%, venous thrombosis by 36%, and total mortality by 17%, but increased diabetes risk by 28 %. On the other hand, in the participants without diabetic risk factors, all parameters decreased significantly with larger drops compare dto those with diabetic risk factors (primary endpoint by 52%; venous thrombosis by 53%; total mortality by 22 %). And, importantly, no elevations in the new onset of diabetes or impairment of glucose metabolism were observed. These results suggested that statins may have more stronger benefits on reduction of cardiovascular risks and glucose metabolisms in individuals without

diabetes compared to those with diabetes. When compared to placebo, the onset of diabetes needed longer duration by 5,4 weeks in rosuvastatin (rosuvastatin, 84.3 weeks vs placebo, 89.7 weeks). The benefits on cardiovascular risk and total mortality in rosuvastatin group were greater than the hazard of the new onset of diabetes [7].

Furthermore, three recent meta-analyses of large-scale placebo-controlled and standard care-controlled trials [82] showed approximately more than 10% increased risk for incident diabetes associated with statin therapy. [83, 84]

On the other, recently the post hoc analysis of ATTEMPT study assesses the incidence of new-onset diabetes over 3.5 years in patients with metabolic syndrome observed no differences in the new onset of diabetes in patients with statins (statins, 0.83 vs. placebo, 1.00/100 patient-years) from the general population [67, 85], and no differences in the new onset of diabetes between individuals with and without diabetic risk factors [84]. New-onset diabetes incidence and CVD events were negligible and not different from what is expected in the general population. [85]

Park *et al.* [9] analysed the linkage of statins and the new-onset diabetes using meta-analysis in published large cohort studies in MEDLINE from 2000 to October 2013 with the following MESH terms and text key words alone or in combination were included: 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, HMG-CoA reductase inhibitors, statins, incident diabetes, new-onset diabetes, insulin resistance, impaired insulin secretion, meta-analysis, cohort study, and observational study written in English. Results of observational studies and meta-analyses show association of incident diabetes with statin use in patients with concomitant risk factors for diabetes. They concluded a possible association between statin use and incident diabetes in patients with underlying diabetes risk factors in available clinical data. Although study data may be insufficient to change the current practice paradigm, clinicians should vigilantly monitor for incident diabetes in patients on statins. Patients with a low risk of CVD and high risk of diabetes should reconsider statin use and focus on lifestyle management. Each statins has different effects on glucose metabolisms, and women and elderly persons are known at higher risk of diabetes. Therefore, various confounders related to adverse events, especially glucose metabolisms, should be considered

Muscoqiuri, *et al.* [86] discussed the effects of statins on insulin sensitivity or insulin secretion, because statins deteriorates glycemic control may accelerate progression to diabetes via molecular mechanisms that impact insulin sensitivity and secretion. The weight of clinical evidence suggests a worsening effect of statins on insulin resistance and secretion, but basic science studies could not find a clear molecular explanation from searches of computerized databases, providing conflicting evidence regarding both the beneficial and the adverse effects of statin therapy on insulin sensitivity.

A number of meta-analyses conducted in recent years have demonstrated that the association is real but causality has not yet been proved [8]. And the underlying mechanisms for this association remain unclear.

In summary, although many clinical studies have demonstrated that statins worsen glucose metabolism or cause the new onset of diabetes, the cardiovascular benefits of statin therapy

overweigh the risk of impairment of glucose metabolism. Clinical practice for statin therapy should not be changed on the basis of the most recent Food and Drug Administration informational warnings in 2012. Therefore, the data suggest the need to treat dyslipidemia and to make patients aware of the possible risk of developing type 2 diabetes or, if they already are diabetic, of worsening their metabolic control.

3. Conclusions

In 2014, Simic and Reiner [87] summarized benefits and side effects of stastins as follow; 1) reduction in cardiovascular mortality and morbidity even in patients with very high risk of cardiovascular disease; 2) myopathy and rhabdomyolysis as most important side effects; 3) liver injury as a side effects, which occurs occasionally but is reversible. On the other hand, statins also improve hepatic steatosis and liver injury in fatty liver diseases; 4) similarly, renal injury as a side effect, but also statins showed protective effects on renal injury [69] and majority of data have shown the beneficial effects on renal function [33, 50-53, 67. 72]. 5) statins increase the incidence of type 2 diabetes, especially in individuals with diabetic risk factors [78]. But the cardiovascular benefits of such a treatment by far exceed this risk. Therefore, currently many guidelines for treatments for dyslipidemia, diabetes concluded that the cardiovascular benefits of statins by far outweight non-cardiovascular harms in patients with cardiovascular risk. However, it should be needed to treat dyslipidemia and to make patients aware of the possible risk of developing type 2 diabetes or, if they already are diabetic, of worsening their metabolic control.

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