UNIT NO. 1

LIPID MANAGEMENT IN DIABETES MELLITUS: A SINGAPORE PERSPECTIVE

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ABSTRACT

Patients with Diabetes Mellitus (DM) have increased risk of atherosclerosis and up to half die during the first myocardial infarction. Primary prevention of cardiovascular disease (CVD) should be a major goal in the management of DM patients. DM patients with the highest risk (established CVD or chronic kidney disease) should have aggressive lipid-lowering therapy. Statin therapy should be the first line of therapy for all DM patients with elevated LDL-C. Ezetimibe can be added if LDL-C target is not reached at maximally tolerated statin dose. Fibrates can be used in DM patients with TG of >4.5 mmol/l (400 mg/dl). The adverse effects from lipid-lowering therapy are low while the benefits of intervention are well proven and significant.

Keywords:
Statins; Very High Risk; High Risk; Macrovascular Complications

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INTRODUCTION

Patients with diabetes mellitus (DM) are at increased risk of atherosclerosis and its consequences. In Singapore, almost 60 percent of those with DM die as a consequence of cardiovascular disease (CVD).[1] The case fatality in diabetic subjects is also higher and up to 50 percent of diabetic patients suffering their first myocardial infarction die during that episode and will never benefit from secondary prevention.[2] Therefore primary prevention of CVD should be a major goal of therapy in the management of patients with DM. The consequences of untreated coronary risk factors in DM patients in Singapore are no different from DM patients elsewhere. Evidence of benefits gleaned from worldwide lipid intervention studies can be applied to the Singapore patients.

One of the key contributors to the accelerated atherosclerosis in DM patients is the dyslipidaemia commonly found among diabetic patients. The United Kingdom Prospective DM study (UKPDS)[3] had shown that good glycaemic control, while effective in reducing micro-vascular complications such as retinopathy and nephropathy, did not significantly reduce the risk of macro-vascular complications like myocardial infarction and strokes. On the other hand, several large studies on cholesterol treatment have clearly demonstrated that diabetic patients had the greatest reduction in coronary events when their cholesterol problems were tackled aggressively.

The CARDS trial[4] studied 2838 diabetic subjects without pre-existing CVD but with the typical cholesterol levels found in diabetic patients (LDL cholesterol about 3.1 mmol/l or 120 mg/dl). At the end of 4 years of treatment with atorvastatin, the risk of getting 1 major cardiovascular event was reduced by 37 percent. Local data from Singapore (National Health Survey 1998) have shown that more than 90 percent of diabetic subjects have cholesterol levels that were deemed undesirable (greater than 2.6 mmol/l or 100 mg/dl). This was surprising, especially in diabetic patients who were concurrently undergoing treatment for their glucose control. Quite often, the focus is on achieving the glucose target and the dyslipidaemia is forgotten.

Just as all diabetic subjects get their HbA1c measured periodically, it is equally important that DM patients are screened for dyslipidaemia at the point of diagnosis and thereafter at least once a year. If the lipids are found to be abnormal, then screening for lipid panels after initiating lipid-lowering therapy should be done more frequently to ensure that lipid targets are met and lipid treatment escalated when necessary.

LIPID PROFILE IN DM PATIENTS

The typical cholesterol profile in a DM patient is usually a marginally elevated LDL cholesterol (LDL-C), high triglyceride (TG) and low levels of HDL cholesterol (HDL-C). Some may conclude incorrectly that because the LDL-C is only marginally above the desirable, it does not indicate increased risk of atherosclerosis. The combination of high LDL-C, low HDL-C and elevated TG may represent a higher risk of atherosclerosis than an isolated elevated LDL-C. Many DM patients also suffer from hypertension and this increases the risk even further.

The Role of Diet and Exercise in Addressing Dyslipidaemia in DM Patients

Diet and exercise remain key pillars in the management of dyslipidaemia among DM patients. They are to be complementary to the pharmacotherapy and not one versus the other. Diet changes can lower the LDL-C as well as the TG by approximately 10 to 20 percent[5]. We must never encourage medications at the expense of dietary and lifestyle changes. Changes in diet would include reducing the intake of red meat, eggs (especially the yolk) and dairy products. Fried food on the other hand will result in high TG. Similarly, consuming large amounts of carbohydrate such as rice, noodles, bread, potatoes, can worsen the diabetes control as well as raise the TG levels.

Exercise does not lower the LDL-C but will reduce the TG and raise the HDL-C. This would translate into substantial benefits

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because the higher HDL-C offers better cardiovascular protection. Exercise also improves the overall wellbeing of the patient, helps in weight control and reduces the cardiovascular risk.

Should All DM Patients be Treated as Coronary Risk Equivalent?

The benefits of statin (HMG-CoA reductase inhibitors) therapy is dependent on an individual's absolute risk of atherosclerotic events. Therefore a 5-year treatment with a statin regimen that lowers LDL-C by 2 mmol/l would be expected to prevent major cardiovascular events in 1000 higher-risk patients for every 10,000 patients treated while it would benefit 500 patients in lower-risk patients.[6] Therein lies the dilemma as to whether all DM patients should be classified as secondary prevention, even for those without pre-existing CVD. There is no worldwide consensus but it would be prudent to separate DM patients into very-high-risk and high-risk categories. Patients with pre-existing CVD and chronic kidney disease[7] should be classified as very-high-risk while other DM patients without pre-existing CVD should be classified as high-risk patients.

Our current guidelines recommend that all DM patients should be classified as coronary risk equivalent and hence no additional risk stratification is needed. However DM patients with exceptionally high CVD risk may be candidates for more aggressive lipid-lowering therapy. Understanding this dilemma and classification is important because the LDL-C target for the very-high-risk should be 2.1 mmol/l (80 mg/dl) while the high-risk DM patients should have LDL-C goal of 2.6 mml/l (100 mg/dl).

Does Statin Therapy Increase the Risk of DM?

Meta-analyses of randomised trials with statins were associated with a 10-percent increased risk of reported DM.[8] Those on more intensive statin regimens were associated with a further 10-percent increased risk of DM. This excess of DM diagnoses appeared soon after the initiation of statin therapy but chiefly among patients who had risk factors for DM (raised body mass index or impaired fasting glucose) but the risk did not get larger as treatment continued. However, we must weigh this increased risk against the cardiovascular benefits of statin therapy, which are substantial. However there are no data to suggest that statin treatment causes deterioration in glycaemic control.

What Are the Priorities in Lipid-lowering Therapy?

Even though the typical dyslipidaemia in Type 2 DM consists of raised LDL-C, elevated TG and low HDL-C, the priority for the physician should always be the LDL-C. Next in priority would be HDL-C and then TG. The exception to this scheme of priorities is in individuals with TG >4.5 mmol/l (400 mg/dl), where fibrate therapy can be started early because of the increased risk of acute pancreatitis.

The choice of lipid-lowering therapy in all Type 2 DM patients with LDL-C >2.6 mmol/l (100 mg/dl) is statins.[9] The dose of statins should be titrated upwards to achieve the LDL-C target. Ezetimibe is an agent that selectively inhibits the intestinal absorption of cholesterol and related plant sterols. When added to a statin, 10 mg of ezetimibe will produce a further 18-percent lowering of the LDL-C. This effect is similar to increasing the dose of the statin by about threefold (e.g. increasing 10 mg simvastatin to 80 mg).[10] The combination of simvastatin and ezetimibe has been shown to reduce cardiovascular events in patients with chronic kidney disease, compared to placebo. In patients with established coronary artery disease, ezetimibe, when added to a statin, produces further lowering of LDL-C and cardiovascular events.[11] Ezetimibe can be used as a second-line therapy in association with statins when the LDL-C target is not achieved with maximal tolerated statin dose, or in patients intolerant of statins or with contraindication to statins.

For patients with LDL-C <2.6 mmol/l (100 mg/dl) and HDL-C <0.9 mmol/l (35 mg/dl), fibrates can be considered as the initial lipid-lowering therapy.[12] If HDL-C remains low (<1 mmol/l or 40 mg/dl) after achieving the LDL-C goal with statins, combination therapy can be considered in selected high-risk patients, such as those with Type 2 DM and existing coronary artery disease. If a combination of statin and fibrate is being used, gemfibrozil should be avoided because gemfibrozil has been shown to adversely affect the metabolism of statins. This has not been demonstrated when statins are used in combination with fibrates.

CONCLUSION

There is a lot of misinformation being received by our patients because of the easy availability of non-peer-reviewed conclusions regarding statin therapy, often based on anecdotal experience rather than on evidence-based medicine. The benefits of lipid-lowering therapies are challenged and discarded while the adverse events are magnified, resulting in many patients taking themselves off therapy. An excellent review by Rory Collins is highly recommended which puts in proper perspective the available data from well-conducted trials about statin therapy.[6] Treatment of 10,000 patients for 5 years with an effective regimen (e.g. Atorvastatin 40 mg) would cause about 5 cases of myopathy, 50-100 new cases of DM, 5-10 haemorrhagic strokes. Furthermore the rare cases of myopathy and muscle-related symptoms attributed to statin therapy generally resolves rapidly when the treatment is stopped. This is the message we must get across to our patients on lipid-lowering treatment.

DM patients are at risk of both micro-vascular as well as macro-vascular disease. Good glycaemic control would reduce the risk of micro-vascular complications but macro-vascular complications such as CVD and myocardial infarction requires aggressive lipid-lowering treatment and tackling other CVD risk factors such as blood pressure and smoking. The evidence showing the benefits of lipid treatments are overwhelming and the safety concerns have been addressed conclusively. Therefore, any DM patient with dyslipidaemia should be considered for therapy.

REFERENCES

1. Ma S, Cutter J, Tan CE, Chew SK, Tai ES. Associations of diabetes mellitus and ethnicity with mortality in a multiethnic Asian population: data from the 1992 Singapore National Health Survey. Am J Epidemiol. 2003;158:543–52.
2. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care. 1998;21:69–75.
3. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837–53. (Erratum in Lancet, 1999;354:602.)
4. Colhoun HM, Betteridge DK, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364:685–96.
5. Bruckert E, Rosenbaum D. Lowering LDL-cholesterol through diet: potential role in the statin era. Curr Opin Lipidol. 2011;22:43–8.
6. Collins R, Reith C, Emberson J, Jane Armitage, Colin Baigent, Lisa Blackwell, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388:2532–61.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Kidney inter., Suppl. 2013;3:259–305.
8. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735–42.
9. Vijan S, Hayward RA. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Ann Intern Med. 2004;140:650–8.
10. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002;40:2125–34.
11. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.
12. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med. 2002;162:2597–604.

LEARNING POINTS

- **DM patients with the highest CVD risk should be managed more aggressively.**
- **Statin should be the first choice of lipid-lowering drug.**
- **The benefits of lipid-lowering therapy are overwhelming and the safety of statins are well proven.**