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Dyslipidemia and Type 2 Diabetes Mellitus: Implications and Role of Antiplatelet Agents in Primary Prevention of Cardiovascular Disease

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1. Introduction

Dyslipidemia is the major risk factors for macrovascular complications leading to cardiovascular disease (CVD) in type 2 diabetes mellitus (T2DM). In addition to this, endothelial dysfunction, platelet hyperactivity, impaired fibrinolytic balance and abnormal blood flow may accelerate atherosclerosis and increased risk of thrombotic vascular events (Colwell & Nesto, 2003). Macrovascular disease is the most common cause of morbidity and mortality in T2DM (Koskinen, 1998). Macrovascular disease is defined as illnesses affecting the larger arteries supplying the heart, brain, and the legs, thereby causing ischemic heart disease, cerebrovascular disease, and peripheral vascular disease (Thompson, 1999). In patients with diabetes, alteration in distribution of lipid increased risk of atherosclerosis. Specifically, insulin resistance and insulin deficiency was identified as phenotype of dyslipidemia in diabetes mellitus (Taskinen, 2003; Krauss & Siri, 2004; Chahil & Ginsberg, 2006). This was characterized with high plasma triglyceride level, low HDL cholesterol level and increased level of small dense LDL-cholesterol (Mooradian, 2008). In these patient also, the increment of free fatty-acid release is due to insulin resistance. With the presence of adequate glycogen stores in the liver, this will promote triglyceride production, which stimulates the secretion of apolipoprotein B (Apo B) and VLDL cholesterol (Mooradian, 2008). Hepatic production of VLDL cholesterol is enhanced due to disability of insulin to inhibit the release of free fatty-acid. Low HDL cholesterol levels were also associated with hyperinsulinemia. There are several associations between dyslipidemia and the increased risk of cardiovascular disease in patients with type 2 diabetes mellitus. Low HDL cholesterol and increased triglyceride levels may contribute to the increased risk of cardiovascular disease. In conjunction with increased small dense LDL cholesterol and low HDL cholesterol levels, further evidence suggests that acceleration of atherosclerosis in diabetes mellitus and insulin-resistant conditions is regulated by hypertriglyceridemia. Nevertheless, the association between LDL cholesterol and CHD risk is stronger compared to the association between hypertriglyceridemia and CHD risk. Type 2 diabetes is also associated with insulin resistance and hyperinsulinemia or syndrome X comprises hypertension, dyslipidemia,

decreased fibrinolysis and increased procoagulation factors (Serrano Rios, 1998). Besides dyslipidemia, platelet abnormalities contributed significantly to increased risk of CVD in these patients. In patients with type 2 diabetes, the platelet abnormalities are due to increased platelet aggregability and adhesiveness (Colwell & Nesto, 2003) and enhanced platelet aggregation activity may precede development of CVD (Halushka et al. 1981, Mandal et al. 1993). It has been well known that management of dyslipidemia in diabetes mellitus includes lifestyle changes such as increased physical activity and dietary modifications. Besides, various antihyperlipidemic agents have been utilized for this purpose. In contrast, antiplatelet agents are recommended mainly for primary and secondary prevention for cardiovascular disease in T2DM. Dyslipidemia is categorized as one of the cardiovascular risk factors besides others (family history CHD, hypertension, smoking, albuminuria) (American Diabetes Association, 2011). Patients with T2DM and having dyslipidemia are eligible for primary prevention of CVD with antiplatelet agents. This chapter will discuss on different types of antiplatelet agents used as primary prevention of cardiovascular disease in patients with T2DM. It will also emphasize appropriate selection of antiplatelet agents pertaining to clinical conditions of patients with T2DM and dyslipidemia.

2. Pathophysiology of dyslipidemia and platelet abnormalities in type 2 diabetes mellitus

Atherogenic dyslipidemia is characterized by three lipoprotein abnormalities: elevated VLDL, small LDL and decreased HDL cholesterol levels, named as atherogenic lipoprotein phenotype (Grundy, 1998). In patients with type 2 diabetes, the prothrombotic state is characterized by increased fibrinogen levels (Imperatore et al 1998), increased plasminogen activator inhibitor (PAI)-1 (Byberg et al., 1998) and abnormalities in platelet function (Trovati et al., 1988). The reason for three aforementioned phenotypes in athrogenic dyslipidemia is the increased free fatty-acid release from insulin-resistant fat cells (Taskinen, 2003; Krauss & Siri, 2004; Chahil & Ginsberg, 2006). The increased flux of free fatty acids into the liver in the presence of adequate glycogen stores promotes triglyceride production, which in turn stimulates the secretion of apolipoprotein B (ApoB) and VLDL cholesterol (Mooradian, 2008). The impaired ability of insulin to inhibit free fatty-acid release leads to enhanced hepatic VLDL cholesterol production (Frayn, 2001) which correlates with the degree of hepatic fat accumulation (Adiels et al., 2007). The increased number of plasma VLDL cholesterol and triglyceride levels decrease the level of HDL cholesterol and increase the concentration of small dense LDL cholesterol (Mooradian, 2008).

Platelet activation commenced with binding of thrombogenic substances (collagen, thrombin, components of atheromatous plaque) to receptors located on the platelet surface (Colwell & Nesto, 2003). Receptor binding triggers a series of events that include hydrolysis of membrane phospholipids, mobilization of intracellular calcium, and phosphorylation of important intracellular proteins (Colwell & Nesto, 2003). There are several platelet abnormalities seen in diabetes patients. Abnormalities of thromboxane A2 (TXA_2) production were among the earliest abnormalities in platelets of diabetes patients. TXA_2 is a potent activator and its synthesis is suppressed by aspirin (Natarajan et al., 2008). Platelets from patients with type 2 diabetes mellitus found to have increased expression of adhesion molecules CD31, CD36, CD49b, CD62P and CD63 (Eibl et al., 2004). Glycemic control

improvement led to a significant decline in their expression (Eibl et al., 2004). In type 2 diabetes patients, platelets increased surface expressionof GP Ib and GP IIb/IIIa (Vinik et al., 2001). GP Ib mediates binding to von Willebrand factor (vWf) which is important in platelet-dependent thrombogenesis (Natarajan et al., 2008). Increased expression of GP IIb/IIIa on platelet surfaces leads to enhanced fibrinogen binding, platelet cross-linking and thrombogenesis (Colwell & Nesto, 2003). In patients with type 2 diabetes, decreased platelet insulin receptor number and affinity responsible for platelet hyperactivity (Vinik et al., 2001). Platelets have been shown to be targets of insulin action as they act as functional insulin receptor for insulin binding and autophosphorylation (Vinik et al., 2001). Insulin reduces platelet responses to the agonists' adenosine diphosphate (ADP), collagen, thrombin, arachidonate and platelet-activating factor. (Natarajan et al., 2008). In patients with type 2 diabetes also, platelets show disordered calcium homeostasis (Li et al., 2001). This may cause hyperactivity including platelet shape change, secretion, aggregation and thromboxane formation (Beckman et al., 2002). Furthermore, the deficiency of magnesium in diabetes has been associated with platelet hyperaggregability and adhesiveness (Gawaz et al., 1994). In type 2 diabetes patients, the reduced vascular synthesis of the anti-aggregants prostacyclin and nitric oxide by endothelium, shift the balance towards aggregation and vasoconstriction (Vinik et al., 2001; Ferroni et al., 2004). In type 2 diabetes patients with acute hyperglycaemia, shear stress-induced platelet activation and P-selection expression (Natarajan et al., 2008). Hyperglycaemia also causes non-enzymatic glycation of platelet membrane proteins resulting in changes in protein structure and conformation, as well as alterations of membrane lipid dynamics (Brownlee et al., 1988; Winocour et al., 1992). This could result in enhanced expression of certain crucial platelet receptors, for instance, P-selectin and GP IIb/IIIa, thus altering platelet activity (Ferroni et al., 2004). Glycated LDL causes an increase in intracellular calcium concentration and platelet nitric oxide (NO) production, as well as inhibition of the platelet membrane Na+/K+-adenosine triphosphatase (Na+/K+-ATPase) activity (Ferroni et al., 2004).

3. Implications of dyslipidemia and platelet abnormality in type 2 diabetes mellitus

In patients with type 2 diabetes mellitus, low HDL cholesterol and high triglyceride levels might contribute to the increased risk of cardiovascular disease (Mooradian, 2008). Based on the Expert panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (2011), hypertriglyceridemia, increased small dense LDL cholesterol and low HDL cholesterol found to be important in accelerating atherosclerosis in diabetes mellitus and insulin-resistant conditions. Abnormal platelet function is another important risk factors for cardiovascular disease in patients with diabetes (Colwell & Nesto, 2003). Atherosclerosis and thrombosis contribute significantly to the increased cardiovascular risk of diabetic patients (Colwell, 1997). The majority of ischemic coronary and cerebrovascular events are precipitated by vessel occlusion caused by atherosclerotic plaque disruption, platelet aggregation, platelet adhesion and thrombosis (Colwell & Nesto, 2003). Several systems that involved vasculature such as platelet, endothelial function, coagulation and fibrinolysis are impaired in patients with diabetes (Jokl & Colwell, 1997). Furthermore, increased platelet aggregability and adhesiveness are due to reduce membrane fluidity, increased intracellular Ca2+ and decreased intracellular Mg2+, increased arachidonic acid metabolism, increased

TXA_2 synthesis, decreased prostacyclin production, decreased NO production, decreased antioxidant levels and increased expression of activation-dependent adhesion molecules (Halushka et al., 1981; Mayfield et al., 1985; Watala et al., 1998; Martina et al., 1998; Trovati et al., 1997; Sarji et al., 1979; Tschoepe, et al., 1997; Leet et al., 1981). For patients with T2DM, the presence of dyslipidemia and platelet hyperactivity justifies the use of antiplatelet agents as primary prevention strategy of CVD.

4. Role of antiplatelet agents in primary prevention of CVD

Increased physical activity, dietary modifications and pharmacologic interventions are the key methods in management of dyslipidemia in type 2 diabetes mellitus (Mooradian, 2008). The Antithrombotic Trialists' Collaboration meta-analysis found that antiplatelet therapy reduces the relative risk of any serious vascular event by 25% in patients at high risk for a cardiovascular (CV) event (Antithrombotic Trialist' Collaboration, 2002). Antiplatelet agents are used for primary and secondary prevention of CVD in type 2 diabetes mellitus patients. Antiplatelet therapy is needed in the management of diabetes mellitus because there is an increase of platelet aggregability and adhesiveness due to platelet and endothelial dysfunction, impaired coagulation cascade, and fibrinolysis process among diabetic individuals compared to nondiabetic individuals (Colwell & Nesto, 2003). Consequently, the balance in normal hemostasis is shifted to favor thrombosis and accelerated atherosclerosis and results in increasing CVD (Colwell & Nesto, 2003). For primary prevention of cardiovascular diseases, type 2 diabetes mellitus patients with high risk acquiring cardiovascular events such as those with family history of cardiovascular disease, hypertension, obesity (BMI > 30 kg/m^2), smoking, dyslipidemia and albuminuria (Colwell, 2004). Several types of antiplatelet agents is being utilized for prevention of CVD which including aspirin, ticlopidine, clopidogrel and glycoprotein (Gp) IIb-IIIa antagonist such as abciximab, eptifibatide and tirofiban (Patrono et al., 2004; American Diabetes Association, 2006; Colwell & Nesto, 2003). Aspirin is one of the most common antiplatelet that been suggested in prevention of CVD in diabetes. Clopidogrel and ticlopidine are theinopyridine antiplatelet agents that generally suggested if patients are contraindicated to aspirin (American Diabetes Association, 2006). In contrast, Gp IIb-IIIa antagonist is usually given to diabetes patients who undergo precutaneous coronary intervention in order to intensify the antiplatelet therapy and to reduce the risk of procedure related thrombotic complication and reoccurrence of CV event (Patrono et al., 2004).

5. Types of antiplatelet

5.1 Aspirin

Aspirin selectively and irreversibly acetylates the COX-1 enzyme, thereby blocking the formation of thromboxane A2 in platelets and leads to inability of platelet to resynthesize COX-1 (Patrono et al., 2005). Aspirin has been used as a primary strategy to prevent CVD in type 2 diabetes due to its effectiveness in atherosclerosis prevention is well established. Various meta-analyses studies and large scale randomized controlled trials in T2DM support that low-dose aspirin therapy should be prescribed as prevention strategy in T2DM, if the contraindication is not exist (Colwell, 2004). Low dose of aspirin inhibits thromboxane production by platelets but has little or no effects on other sites of platelet activity (Colwell & Nesto, 2003). Several randomized controlled trials had been designed to assess the

efficacy of aspirin in primary prevention of CVD which included Primary Prevention Project (PPP), US physicians' Health Study (USPHS), Early Treatment of Diabetes Retinopathy Study (ETDRS), Hypertension Optimal Treatment Trial (HOT), British Male Doctors' Trial (BMD) and the Thrombosis Prevention Trial (TPT) (Colwell & Nesto, 2003; Hayden et al., 2002). In Primary Prevention Project (PPP), a low dose aspirin (100 mg/day) was evaluated for the prevention of cardiovascular events in individuals with one or more of the following conditions such as hypertension, hypercholesterolemia, diabetes, obese, family history of premature myocardial infarction or being elderly. After a mean of 3.6 years follow-up, aspirin was found to significantly lower the frequency of cardiovascular death (from 1.4 % to 0.8 %); relative risk (RR) 0.56 [confidence interval (CI) 0.31-.99] and total cardiovascular events (from 8.2 to 6.3% ; RR 0.77 [0.62-0.95]). This trial involved large sample size (n = 4495) with the largest proportion of patients with diabetes mellitus (17%) (Collaborative Group of the Primary Prevention Project, 2001). Overall, PPP provides evidence to prove the efficacy of aspirin in diabetes; though participants were not blinded and were not given placebo pills. Additionally, a meta-analysis done by Hayden et al., (2002) also rated the quality of PPP as "fair" if compared to the rest of studies. In addition to PPP, a 5 years primary prevention trial in 22 701 healthy men; included 533 men with diabetes was conducted in US Physicians' Health Study (USPHS) in which a low-dose aspirin regimen (325 mg every other day) was given to treated group compared with placebo. A total of 44% significant risk reduction in CVD treated group was noted and the subgroup analyses in the diabetes reveals a reduction in myocardial infarction from 10.1 % (placebo) to 4.0 % (aspirin), yield a relative risk reduction of 0.39 for the diabetes men on aspirin therapy (Steering Committee of the Physicians' Health Study Research Group, 1989). Researcher and participants were blinded in this trial. In contrast with PPP, women were included in the study populations (2583 out of 4495 sample sizes). Hence, this study was more reliable compared to previous ones even though only 2% of the study population was diagnosed with diabetes. The Hypertension Optimal Treatment Trial (HOT) also examined the effects of low dose of aspirin (75 mg/day) versus placebo in 18 790 hypertension patients and 8% of them had diabetes. Results showed that aspirin significantly reduce cardiovascular event by 15% and myocardial infarction by 36% (Hansson et al., 1998). The HOT trial was another primary prevention study that included women, which was 46.6 % from total study population. Colwell (2004) commended that this study provided further evidence for the efficacy and safety of aspirin therapy in diabetes with systolic blood pressure less than 160 mmHg. Hayden et al., (2002) was in agreement with Colwell (2004) and concluded that HOT was a "good" quality of trial in their meta-analysis. Despite that, these findings were mirrored by Early Treatment of Diabetes Retinopathy Study (ETDRS) where they reported that although aspirin did not prevent progression of retinopathy but it did produce a significant reduction in risk for myocardial infarction (28%) over 5 years (P=0.038). This study may viewed as mixed primary and secondary prevention trials since those enrolled had a history of myocardial infarction and less than 50% had elevated blood pressure and history of CVD (ETDRS Investigators 1992). Conversely, the British Male Doctors' Trial (BMD) had conflicting results regarding aspirin effects in reducing the risk for myocardial infarction and adverse effects such as gastrointestinal bleeding and hemorrhagic stroke to diabetes patients. A total of 39 % of participants were discontinued therapy during the study due to adverse effect of aspirin (Hayden et al., 2002). Similar to PPP trial, participants in this study were not blinded thus results may be varies. Following this, a meta-analysis of these

five randomized clinical trials (except ETDRS) was performed by Hayden et al., (2002) and systematic reviews on nine articles about the effect of aspirin on gastrointestinal bleeding and hemorrhagic stroke were conducted. They concluded that the net benefit of aspirin increase with CV risk. Nonetheless, this meta-analysis was found to have selection bias due to exclusion of 2 large trials that examined the effects of aspirin in patients with diabetes or stable angina. Sanmuganathan et al., (2001) also reached similar estimates of the beneficial effects of aspirin in primary prevention of CVD. The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was the first prospectively designed trial to evaluate the use of aspirin (81 mg or 100 mg) in the primary prevention of cardiovascular events in patients with type 2 diabetes (n = 2539) aged 30–85 years in Japan (Ogawa et al., 2008). Among patients aged > 65 years (n =1363), aspirin was associated with a 32% reduction in the risk of the primary end point (6.3 vs. 9.2%; P = 0.047). Furthermore, in aspirin-treated patients, the incidence of fatal coronary and cerebrovascular events was significantly lower by 90% (0.08 vs. 0.8%; P = 0.0037). Paradoxically, there were no differences in nonfatal coronary and cerebrovascular events. Aspirin was well tolerated, with no significant increase in the composite of hemorrhagic stroke and severe gastrointestinal bleeding (Angiolillo, 2009). The outcome of this study was in opposite with the current recommendations on aspirin usage in primary prevention of CVD in diabetes patients (Angiolillo, 2009). However, the ASCEND and ACCEPT-D study are two ongoing trials will provide further insights to the appropriateness of aspirin usage in primary prevention of CVD in patients with diabetes. Another recent trial (POPADAD), failed to show any benefit with aspirin or antioxidants in primary prevention of cardiovascular events (Belch, 2008). The outcome of the study could be due to small number of patients with low event rates. A study on the utilization of antiplatelet therapy in type 2 diabetes patients revealed that many of the eligible patients did not receive the drugs as primary prevention strategy for CVD (Huri et al., 2008). Therefore, the recommendations on aspirin usage in primary prevention of CVD in type 2 diabetes patients must be fully justified after taking consideration against the benefit versus risk of its use. In another words, the recommendations should be base on individual patients' assessment and clinical judgment. Proper use of aspirin in primary prevention of CVD in type 2 diabetes patients may result in long-term benefits.

5.2 Clopidogrel

Clopidogrel is another type of antiplatelet agents used in primary prevention of CVD in type 2 diabetes when patients are intolerant to aspirin. It inhibits ADP-induced platelet aggregation by blocking the purinergic receptors and therefore prevents the activation of the GpIIb-IIIa receptor and subsequent binding to fibrinogen (Colwell & Nesto, 2003). Clopidogrel is preferable compared to ticlopidine because of its safety profile (Savi & Herbert, 2005; Bertrand et al., 2000). Nevertheless, the information regarding the usage of clopidogrel in primary prevention of CVD is limited than for secondary prevention of CVD in diabetes patients. Even though clopidogrel may be slightly more effective than aspirin, the size of any additional benefits is statistically uncertain and it has not been granted a claim of superiority against aspirin (Patrono et al., 2004). However, the publication of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) recently had led to FDA approval of a new indication for clopidogrel in patients with acute coronary syndromes without ST-segment elevation (Patrono et al., 2004).The CURE trial examined CV

outcomes with clopidogrel plus aspirin versus aspirin alone in patients with acute ischemic heart disease (IHD) (CURE Steering Committee, 2001). These findings demonstrated that clopidogrel has beneficial effects in patients with acute coronary syndromes without ST-segment elevation thus can be generalized as the study sample size (n =12,562) was large and patients were recruited from 482 centers in 28 countries. This trial also showed that 3.7% of patients in this combination therapy group had major bleeding and it was significant more compared with those solely on aspirin but there was no increase in life-threatening bleeds (CURE Steering Committee, 2001). Hence, a loading dose of 300mg clopidogrel should be used in this setting followed by 75 mg daily (Patrono et al., 2004). Bhatt et al., (2002) concluded that clopidogrel is an effective drug for secondary prevention in diabetes. Therefore, previous studies clearly justified the use of dual anti platelet therapy with aspirin and clopidogrel for secondary prevention of CVD in diabetes patients. Its role in primary prevention of CVD in diabetes patients is vague since no study has directly measure the outcome for this purpose.

5.3 Ticlopidine

Ticlopidine also inhibit ADP-induced platelet aggregation with no direct effects on the metabolism of arachidonic acid (Patrono, 1998). It has slower antiplatelet effect compared with clopidogrel (Patrono et al., 2004). Ticlopidine in Microangiopathy of Diabetes (TIMAD) study was conducted by involving 435 patients with nonproliferative diabetes retinopathy to evaluate for its effects on macrovascular disease in diabetes patients. Patients were randomized to receive ticlopidine, 250 mg twice daily and were followed up to 3 years. Ticlopidine was found significantly reduced annual microaneurysm progression by 67% and overall progression of retinopathy was significantly less severe with ticlopidine (TIMAD Study Group, 1990). However, this study was not designed to evaluate effect of ticlopidine on cardiovascular events. There are limited studies done on effect of ticlopidine in prevention of CVD in diabetes. In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent myocardial infarction (Patrono et al., 2004). Even though ticlopidine has lower cost compared to clopidogrel, (Drug Formulary University Malaya Medical Centre, 2005; Patrono et al., 2004), its role in primary prevention of CVD in type 2 diabetes patients have not been established.

5.4 Dipyridamole

Dipyridamole inhibits platelet cyclic-3′,5′-adenosine monophosphate and cyclic-3′, 5′-guanosine monophosphate phosphodiesterase (Natarajan et al. 2008). Overview of 25 trials among approximately 10000 high risks of CVD patients with the use of dipyridamole and aspirin, it was found that the addition of dipyridamole to aspirin has not been shown clearly to produce additional reductions in serious vascular events (Patrono et al., 2004). However, one of 25 trials suggested that there may be a worthwhile further reduction in stroke (Patrono *et al.* 2004). Patrono et al., (2004) also suggested that the combination of low dose aspirin and extended release dipyridamole (200 mg twice daily) is considered an acceptable option for initial therapy of patients with non-cardioembolic cerebral ischemic events and not in patients with ischemic heart attack. The benefits of dipyridamole in patients with diabetes have not been reported (Natarajan et al., 2008). Specifically, there are limited studies or trials conducted to examine the role of dipyridamole for primary and secondary prevention of CVD amongst T2DM patients.

5.5 GP IIb/IIIa inhibitors

The platelet glycoprotein (GP) IIb/IIIa complex receptor antagonists block activity at the fibrinogen binding site on platelet (Colwell & Nesto, 2003). These agents are useful in type 2 diabetes patients with acute coronary syndrome and in those undergoing percutaneous coronary interventions (Colwell & Nesto, 2003). These agents are administered intravenously with a rapid onset of action and short half-life (Natarajan et al., 2008). Numerous studies have been performed comparing various GP IIb/IIIa inhibitors. Currently, three different GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) are approved for clinical use. This group of drugs was mainly study for secondary prevention of CVD in diabetes patients. Evidence from three trials revealed that among 1,262 diabetes patients, use of these agents was associated with reduction in mortality from 4.5% to 2.5% (p=0.031) (Bhatt et al., 2000). In another meta-analysis of six large trials, with 6,458 patients with diabetes and acute coronary syndromes, GP IIb/IIIa inhibitor therapy was associated with a significant mortality reduction at 30 days, from 6.2% to 4.6% CI(0.59-0.92, p=0.007) (Roffi et al., 2001). Nonetheless, the role of GP IIb/IIIa inhibitors in primary prevention of CVD in type 2 diabetes mellitus has not been justified; therefore it is not recommended for this purpose.

6. Appropriate selection of antiplatelet agents for primary prevention of CVD in type 2 diabetes patients

Among all choices, there are considerations to be taken into account before types of antiplatelet agents chosen. According to American Diabetes Association (2011), aspirin (75-162mg/day) should be considered for primary prevention of cardiovascular disease in type 2 diabetes patients for men (>50 years) and women (>60 years) with at least one additional major risk factor (family history of cardiovascular disease, hypertension, smoking, dyslipidemia or albuminuria). The other types of antiplatelet agents either alone or combination with aspirin therapy has no established role in primary prevention of cardiovascular disease in type 2 diabetes patients. In contrast, aspirin should not be recommended for CVD prevention for diabetes patients with low CVD risk (10-year CVD risk <5%, such as in men <50 and women <60 years of age with no additional CVD risk factors, since the potential adverse effects from bleeding likely outweigh the potential benefits (ADA, 2011). A same recommendation goes to type 2 diabetes patients with multiple other risk factors (e.g. 10-year risk 5-10%), in which clinical judgment is required (American Diabetes Association, 2011).

7. Monitoring of aspirin efficacy and adverse effects

Aspirin once daily (75-100 mg) is recommended in primary prevention of CVD in type 2 diabetes patients when antiplatelet prophylaxis has a favorable benefit/risk profile (Patrono et al., 2004). For effectiveness of primary prevention strategy, patients should be followed on a regular basis and examined for signs and symptoms of any cardiovascular diseases. In consideration of dose-dependent GI toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting (Patrono et al., 2001). Aspirin should not be given to patients with gastrointestinal ulcerations; best tolerated after food. In conclusion, bleeding and gastrointestinal complications are the most common adverse effects of aspirin. Thus, the patients on aspirin should be monitored for stomach pain, heartburn, nausea and bleeding tendency.

8. Conclusion

Dyslipidemia is one of the risk factors for acquiring cardiovascular disease in patients with type 2 diabetes. In absent for contraindication, type 2 diabetes patients with dyslipidemia are eligible for primary prevention of cardiovascular disease although the routine use has not been documented. Aspirin plays a key role in primary prevention strategy of cardiovascular disease in type 2 diabetes patients. With limited studies and evidence for other antiplatelet agents, their role in primary prevention has not been established.

9. Summary

Dyslipidemia is one of the major risk factors for macrovascular disease leading to CVD in type 2 diabetes.

In type 2 diabetes patients with dyslipidemia, alteration in lipid distribution and platelet abnormalities increased risk of acquiring CVD.

Patients with type 2 diabetes with one of the following; dyslipidemia, family history of coronary heart disease, hypertension, smoking and albuminuria are at increased risk of CVD, thus eligible for primary prevention strategy of CVD.

With limited evidence, proper justification and clinical judgments of benefit versus risk, aspirin plays a key role as antiplatelet agent in primary prevention of CVD in patients with type 2 diabetes with dyslipidemia.

Patients with type 2 diabetes and dyslipidemia receiving aspirin for primary prevention strategy should be monitored for effectiveness of treatment (sign and symptoms of CVD) and adverse effects (stomach pain, heartburn, nausea and bleeding tendency).

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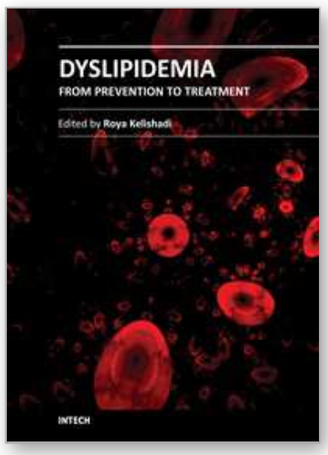

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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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