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Pharmacological Effects of Atorvastatin in Platelet Function and Plaque Rupture

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ABSTRACT

Platelets are a prime reason for causing cardiovascular disease (CVD). After atherosclerotic plaque rupture, platelets can form pathogenic, formation of blood clot which leads to various cardiovascular events. The beneficial effect of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase inhibitors reduces CVDs clinically. The objective of this review is the pharmacological benefit of atorvastatin in CVD by platelets and plaque rupture due to high levels of cholesterol.

INTRODUCTION

Cardiovascular disease (CVD) is a major health problem and the prevalence of CVD is highest in the industrial world for last few decades (Vijaya Anand *et al.*, 2008). Platelets are specialized cells, which involved in the formation of blood clots and circulating platelet levels are related to the formation of mural thrombus at the site of plaque rupture and vascular injury (Lacoste *et al.*, 1995; Willerson *et al.*, 1989). Platelet aggregation and plaque rupture can be occurred due to high levels of cholesterol which results in CVD. The risk of cardiovascular events can be reduced by atorvastatin therapy through reduction of plasma total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels (Vijaya Anand *et al.*, 2009).

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Hypercholesterolemia may be related an increased platelet reactivity. This may leads the rise of the cholesterol/phospholipid ratio in platelets. The other possible mechanisms which include an increase in the biosynthesis of thromboxane A_2, the density of platelet α_2-adrenergic receptor, and also platelet cytosolic calcium (Hackeng *et al.*, 1999).

Statins induced the reduction of platelet activity has been described as a positive effect exerted by statins on the thrombotic vascular events. Puccetti *et al.* (2002) suggest a different impact of several statins (simvastatin 20 mg/day, atorvastatin 10 mg/day, fluvastatin 40 mg/day and pravastatin 40 mg/day) on platelet function, which is initially related to interference with platelet-associated-LDL cholesterol rather than LDL cholesterol reduction. Simavastatin ($p < 0.001$), atorvastatin ($p < 0.001$), fluvastatin ($p < 0.01$) and pravastatin ($p < 0.05$) reduce the activity of platelet. This review particularly focuses the role of atorvastatin in platelet and plaque rupture due to abnormal level excess cholesterol.

ATORVASTATIN AND PLATELETS FUNCTION

Platelets play a vital role in the progression of CVD (Fitzgerald *et al.,* 1986). Hypercholesterolemia is correlated with increases in platelet reactivity (Opper *et al.,* 1995). These abnormalities are associated with increases in the cholesterol/phospholipid ratio in platelets. Additional potential mechanisms include increases in thromboxane A2 (TXA2) biosynthesis (Notarbartolo *et al.,* 1995), platelet α^2-adrenergic receptor density (Baldassarre *et al.,* 1997) and platelet cytosolic calcium (Le Quan Sang *et al.,* 1995). Atorvastatin had a marked reduction effect on platelet aggregation (Tekten *et al.,* 2004). Atorvastatin therapy can improve hemorheological parameters and platelet aggregation endothelial dysfunction (Szapary *et al.,* 2004). Combining clopidogrel with atorvastatin in the healthy individuals led to a reduction in ADP-induced platelet p-selectin exposure. Pretreatment with atorvastatin reduces platelet reactivity before administration of clopidogrel (Piorkowski *et al.,* 2004).

Atorvastatin and aspirin therapy in the early onset of the acute event, notably reduced persistent TXA (2) and TXA (2)-dependent aspirin resistance. This may be contributing to the clinical benefit of atorvastatin in patients with myocardial infarction (Santos *et al.,* 2009). Among percutaneous coronary intervention treated patients with high on-treatment platelet reactivity during administration of both atorvastatin and clopidogrel, switching to a non-CYP3A4-metabolized statin significantly decrease platelet reactivity. This switching effect seems to be similar irrespective of the type of non-CYP3A4-metabolized statin (Park *et al.,* 2012).

Therapy with statins successfully modifies ADP-induced platelet aggregation in hyperlipidemic patients and does not affect ADP-induced platelet adhesion to fibrinogen as well as platelet aggregation induced by collagen or ristocetin (Sikora *et al.,* 2013). Moscardo *et al.* (2013), reported the direct downregulation with atorvastatin and simvastatin of platelet cPLA2 activity through effects on calcium, Mitogen-activated protein kinases (MAPK) and decrease TXA2 synthesis, which induced by collagen.

Statins significantly reduce mean platelet volume (MPV) (Sivri *et al.,* 2013). The expression of platelets CD62p and PAC-1 is increased in HNC (normal high-density lipoprotein cholesterol) patients. The surface expression of platelets CD62p and PAC-1 is greater among HLC (low levels of high-density lipoprotein cholesterol) patients than among control patients. After atorvastatin treatment, the expression of CD62p and PAC-1 decreased significantly. The reduction of high-density lipoprotein (HDL) cholesterol and increased platelet activation is seen in patients with high levels of LDL cholesterol (Chan *et al.,* 2015).

High platelet reactivity during co-administration of clopidogrel and a CYP3A4-metabolized statin (i.e. atorvastatin) can be lowered (Pelliccia *et al.,* 2014). The MPV and red cell distribution width (RDW)is associated with an increased cardiovascular risk. There is an association between MPV, RDW and lipoprotein sub-fractions. After 12 weeks of treatment with atorvastatin, MPV and RDW values altered in hypercholesterolemic patients, shows atorvastatin as strongest lipid-lowering effect (Kucera *et al.,* 2015).

In patients suspected with CVD, urinary 11-dehydro (dh) thromboxane B2 (TXB2) was determined. High thrombin-induced platelet-fibrin clot strength (TIP-FCS) indicates elevated 11-dh TXB2 associated with a prothrombotic state. Atorvastatin and aspirin therapy are major treatments for coronary artery disease (CAD) (Bliden *et al.,* 2014).Recent studies reveal that in the thrombotic process the reactive oxygen species (ROS) are implicated. Atorvastatin are associated to redox signaling interfering, inhibition of platelet formation of NADPH oxidase-derived ROS, thus exhibit antiplatelet effects atorvastatins possess antithrombotic effects, and it accounts for the reduction of thrombotic-related vascular outcomes (Violi *et al.,* 2014).

ATORVASTATIN AND PLAQUE STABILITY

Plaque rupture is a main reason of acute coronary syndrome (ACS) (Libby, 1995). The atherosclerotic lesion comprises highly thrombogenic substances in the lipid core that are separated by a fibrous cap from the bloodstream (Fernandez-Ortiz *et al.,* 1994). Ulceration of the fibrous cap ultimately leads to plaque rupture and ensuing thrombosis (Fuster *et al.,* 1990). Collagen is the major constituent of fibrous caps, since macrophages are capable of degrading the collagen-containing fibrous cap; they play a significant role in the progress and subsequent stability of atherosclerotic plaques (Shah *et al.,* 1995).

Certainly, degradation of the plaque matrix seems to be most active in regions with rich macrophage (Fuster *et al.,* 1995). Secretion of Matrix metallopeptidases (MMPs) by activated macrophages may weaken the fibrous cap, mostly at the "vulnerable" shoulder region where the fibrous cap joins the arterial wall (Henney *et al.,* 1991). This weakened fibrous cap possibly leads to plaque instability, rupture and consequently thrombosis (Davies *et al.,* 1995). Intensive statin treatment can improve plaque stability by decreasing the plaque size or by altering the physiochemical properties of the lipid core (Koh *et al.,* 2000; Fukumoto *et al.,* 2001).

The plaque-stabilizing properties are mediated through a combined decrease in lipids, macrophages as well as MMPs (Crisby *et al.,* 2001). These effects of statins may reduce the occurrence of ACS by reducing the tendency for plaque to rupture and may elucidate the rapid time course of event reduction in high risk patients for recurrent coronary ischemia in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) (Schwartz *et al.,* 2001) and the Pravastatin or Atorvastatin Evaluation and Infection trials (PROVE-IT) (Cannon *et al.,* 2004).

The benefits of early statin treatment to stabilize culprit lesions in ACS will directed to an increase in the proportion of coronary patients who will receive this favorable therapy (Waters *et al.,* 2001). Shimojima *et al.* (2012) results confirmed that plaque composition and volume might be changed within 3 weeks following intensive lipid lowering therapy. This may explain acute effects of statins in the treatment of ACS.

Cyclooxygenase (COX)-2 expressions is increased in inflammation and angiogenesis and also in atherosclerotic plaques, where it co-localizes with MMPs involved in weakening of the fibrous cap. The regulation of COX-2 and MMP-9 expression advocates the involvement of a Rho-dependent pathway. In the human vascular endothelium, simvastatin and atorvastatin reduce COX-2 and MMP-9 expression and activity. Through this mechanism, statins concern an anti-angiogenic effect may possibly contribute to the cholesterol-lowering-unrelated protective efficiency of statins against plaque inflammatory angiogenesis as well as rupture (Massaro *et al.*, 2010).

In the treatment of hyperlipidemia, the statins have certain advantageous effects which include plaque stability, enhanced endothelial function, decreased oxidative stress and inflammation, to the further side of their lipid-lowering effect in plasma. The impact of atorvastatin has been evaluated on the structural/mechanical properties of erythrocyte and the lipid peroxidation in dyslipidemics. The atorvastatin treatment reduces the lipid peroxidation in plasma and erythrocytes and enhances plasma total antioxidant capacity (Uydu *et al.*, 2012).

These observations confirmed the lipid lowering action atorvastatin may contribute to plaque stability by decreasing the size of the plaque or by altering the lipid core physiochemical properties. This plaque-stabilizing properties of atorvastatin may be mediated by the reduction of lipids. These effects of atorvastatin may reduce the incidence of ACS and an intensive lipid lowering therapy provides greater protection against major cardiovascular events a (Cannon *et al.*, 2004).

CONCLUSION

In general, the cholesterol reduction by atorvastatin is the predominant therapeutic result underlying their beneficial effects in CVD. The effects result from the combine action on lipid lowering with positive effects on the clinical condition to normal in both plaque stabilization and platelet aggregation. This provides the important information on how to maximize the pleiotropic benefits of atorvastatin in the patients at the risk for CVD.

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