Pharmacological basis of different targets for the treatment of atherosclerosis

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Received: August 19, 2005; Accepted: September 20, 2005

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Abstract

The development of atherosclerotic plaque is a highly regulated and complex process which occurs as a result of structural and functional alterations in endothelial cells, smooth muscle cells (SMCs), monocytes/macrophages, T-lymphocytes and platelets. The plaque formation in the coronary arteries or rupture of the plaque in the peripheral vasculature in latter stages of atherosclerosis triggers the onset of acute ischemic events involving myocardium. Although lipid lowering with statins has been established as an important therapy for the treatment of atherosclerosis, partially beneficial effects of statins beyond decreasing lipid levels has shifted the focus to develop newer drugs that can affect directly the process of atherosclerosis. Blockade of renin angiotensin system, augmentation of nitric oxide availability, reduction of Ca²⁺ influx, prevention of oxidative stress as well as attenuation of inflammation, platelet activation and SMC proliferation have been recognized as targets for drug treatment to control the development, progression and management of atherosclerosis. A major challenge for future drug development is to formulate a combination therapy affecting different targets to improve the treatment of atherosclerosis.

Keywords: atherosclerosis • lipid lowering agents • renin angiotensin system • oxidative stress • inflammation

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Reprinted from:

Journal of Cellular and Molecular Medicine

Published by:
the CMM Foundation

Introduction

Atherosclerosis, the underlying cause of coronary artery disease (CAD), peripheral vascular disease and stroke, is the principle entity responsible for morbidity and mortality in Western societies [1]. Several epidemiological and experimental studies have identified that hypercholesterolemia, hypertension, diabetes mellitus, hyperhomocysteinemia, Chlamydia pneumoniae infection, genetic abnormalities as well as life style factors such as stress, physical inactivity and cigarette smoking are the major risk factors associated with the development of atherosclerosis [2, 3]. Primary and secondary prevention trials with 3-hydroxy-3-methyl glutaryl Coenzyme A (HMG-CoA) reductase inhibitors /statins, in a wide variety of populations including patients with or without established CAD as well as patients with moderate and severe hypercholesterolemia, have demonstrated that lowering plasma low-density lipoprotein (LDL) cholesterol levels is the mainstay for the prevention of atherosclerosis progression and the reduction of coronary events [4]. However, none of these clinical trials with different statins have achieved the optimal reduction in LDL concentration (<100 mg/dl) for high-risk patients as recommended by the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines [5]. It is pointed out that high doses of statins are needed for aggressive lipid lowering but these were found to have a greater risk of causing adverse effects [6]. In addition, the increased cost for employing statins for achieving optimal reduction in LDL cholesterol concentration is a real challenge for the health care professionals [7, 8]. Recently, because of the pleiotropic effects of statins including maintenance of endothelial function, reduction of inflammatory response, attenuation of smooth muscle cell (SMC) proliferation, prevention of oxidative stress and stabilization of plaque, the importance of other target sites other than LDL-cholesterol lowering have been suggested [9, 10]. Furthermore, the awareness of the multi-factorial nature of the disease with alterations in cellular elements such as endothelium, monocytes/macrophages, SMCs, T-lymphocytes and platelets as well as the involvement of various factors released from these cellular components leading to inflammation has revealed the potential novel drug targets for the prevention of atherosclerosis [11] as shown in Fig. 1.

Although atherosclerosis at different locations in the body is manifested by a variety of associated events (Table 1), the underlying mechanisms leading to these events seem to be similar. Various pharmacological therapies have been designed to reduce the risk, development and progression of the atherosclerotic plaque. In addition, different approaches have been pursued for the prevention of the complications arising after rupturing of atherosclerotic plaques. Accordingly, this article presents a comprehensive overview of the existing therapies for the treatment of atherosclerosis in addition to exploring areas of novel pharmacologic targets for the development of improved therapeutic strategies for this devastating disease. It is pointed out that the major thrust of the pathogenesis of atherosclerosis centers around the levels of high-density lipoproteins (HDL) and LDL cholesterol and thus the current therapies are based on lowering the levels of plasma cholesterol. The present article emphasizes the importance of other mechanisms such as oxidative stress, intracellular Ca^{2+} overload, vascular inflammation and cell proliferation, which are suggested to form the basis of future therapies for atherosclerosis.

Lipid modification as a target for the treatment of atherosclerosis

Hypercholesterolemia can directly or indirectly cause cardiac dysfunction. The direct effects of high levels of cholesterol are associated with changes in the activities of the cardiac sarcolemmal (SL) membrane enzymes including $\text{Na}^+\text{-K}^+\text{-ATPase}$, $\text{Mg}^{2+}\text{-ATPase}$, $\text{Ca}^{2+}\text{-pump ATPase}$, $\text{Ca}^{2+}\text{-dependent K}^+$ channels and $\text{Na}^+\text{-Ca}^{2+}$ exchanger [12]. In addition, a decrease in the sarcoplasmic reticulum (SR) $\text{Ca}^{2+}\text{-ATPase}$ mRNA and protein content and concomitant reduction in SR Ca^{2+} -uptake after cholesterol-rich diet intake has been linked with cardiac systolic and diastolic dysfunction [13]. An increase in the ratio of β myosin heavy chain to α myosin heavy chain has also been related to the cholesterol-induced direct effects on the heart [13]. Furthermore, high cholesterol-induced compositional, structural and functional changes in the arterial SMCs participate in the progression of atherosclerosis [14, 15]. Endothelial dysfunction mediated by reduction in synthesis and augmented destruction of nitric oxide (NO), a known

Fig. 1 Diagrammatic representation of major mechanisms involved in the development of atherosclerosis and various drugs for the treatment of the disease.

Table 1 Different sites and associated events during the development of atherosclerosis

	Site	Event
1	Coronary arteries	Ischemic heart disease
2	Peripheral arteries	Arterial occlusive disease
3	Cerebral arteries	Stroke
4	Renal arteries	Kidney failure
5	Aorta	Aortic aneurism

vasorelaxing agent, has also been demonstrated to occur in response to high levels of cholesterol [12]. On the other hand, the indirect effects of cholesterol are due to its conversion to oxidized LDL (OxLDL), which is a major stimulant for SMC proliferation, monocyte adhesion and migration as well as subsequent foam cell formation [16]. A schematic representation of direct and indirect effects of cholesterol for the development of atherosclerosis is shown in Fig. 2. Various therapeutic strategies that target lowering of

LDL-cholesterol or augmentation of high density lipoprotein (HDL)-cholesterol have been employed to prevent the development of atherosclerosis.

HMG-CoA reductase inhibitors

HMG-CoA inhibitors/statins prevent the conversion of HMG-CoA to mevalonate and subsequent biosynthesis of cholesterol [17]. The data obtained from 4S (Scandinavian Simvastatin Survival Study) [18], WOSCOPS (West of Scotland Coronary Prevention Study Group) [19], CARE (Cholesterol and Recurrent Events) [20], LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) [21] and AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) [22] have clearly established the role of statins such as simvastatin, pravastatin and lovastatin in preventing the progression of atherosclerosis in a wide range of patients. Although 25-30% reduction in LDL-cholesterol was observed, none of these clinical trials obtained the optimal lowering of LDL concentration recommended for high-risk patients [23]. In fact, the

Fig. 2 Direct and indirect effects of cholesterol participating in the development of atherosclerosis. LDL: low density lipoproteins; HDL: high density lipoprotein.

results of the REVERSAL (Reversing Atherosclerosis with Aggressive Lipid Lowering) [24] and the AVERT (Atorvastatin versus Revascularization Treatment) [25] clinical trials have emphasized that aggressive statin therapy has a greater impact in preventing the progression of atherosclerosis as well as the incidence of newer coronary events. Recently the results of PROVE IT-TIMI 22 (The Pravastatin or Atorvastatin Evaluation and Infection Therapy- Thrombolysis in Myocardial Infarction 22) trial have shown that intensive lipid lowering with high doses of atorvastatin provide greater protection against mortality or major cardiovascular events after acute coronary syndrome without any risk of complications from the therapy [26, 27]. On the other hand, studies including the HPS (Heart Protection Study) [28] and the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) [29] clinical trials have suggested that all CAD patients, irrespective of their LDL-cholesterol levels, can obtain benefit from simvastatin and atorvastatin therapy, respectively. A subgroup analysis of the WOSCOPS and CARE trials has reported that aggressive reduction of LDL-cholesterol is not beneficial in preventing the development of CAD [19, 20]. In fact, a 2-4 fold increase in the statin dose does not further reduce LDL levels significantly [6]. Although some of the clinical benefits of statins have been observed to be independent of cholesterol lowering [9, 10], the cost effectiveness of the therapy

and the adverse outcomes associated with the continued use of a specific type of statin or combination of statins with other lipid-lowering agents remains to be a major concern in clinical practice [30].

Cholesterol absorption inhibitors

It has been reported previously that two-third of the total cholesterol is synthesized in the body, whereas the remainder comes from the intake of food. Since statins can only block the biosynthesis of cholesterol, there is an ample scope for the agents, which can prevent the absorption of dietary cholesterol [31]. Ezetimibe (Sch-58235) has been recognized as the first agent in a class of novel cholesterol absorption inhibitors, which prevent the absorption of cholesterol from lumen of the intestine into the enterocytes [31, 32]. Co-administration of ezetimibe with statins in patients with primary hypercholesterolemia caused a significant reduction in LDL-cholesterol, triglycerides and an increase in HDL-cholesterol in comparison to the treatment of statins alone [33]. In addition, combination of ezetimibe with low doses of statins was as effective in lowering LDL-cholesterol as were high doses of statins [33]. Davidson and Toth [34] have suggested that for elderly patients, who have a higher risk of developing side effects due to high doses of statins, addition of ezetimibe to moderate doses of statins would be more efficacious than increasing the dose of statins alone.

Peroxisome proliferative activator receptor- α (PPAR- α) activators

The fibrates, gemfibrozil and fenofibrate, which have been shown to activate PPAR- α , cause a significant decrease in serum triglyceride and increase in HDL-cholesterol levels [5]. The results of the VA-HIT (Veterans Affairs Cooperative Studies Program HDL-Cholesterol Intervention Trial) and the Helsinki Heart Study have reported that fibrates attenuate atherosclerosis and reduce the incidence of cardiovascular death, myocardial infarction (MI), and stroke in CAD patients. In addition, the Diabetes Atherosclerosis Intervention Study (DAIS) has demonstrated that fibrates prevent angiographic progression of CAD in diabetic patients [35].

Acyl-cholesterol acyl transferase (ACAT) inhibitors

The esterification of cholesterol is catalyzed by the enzyme ACAT, which is involved in the metabolism and absorption of cholesterol from the intestine, secretion of very low-density lipoprotein (VLDL) particles from the liver, and the development of atherosclerotic lesions [36]. Recently, avasimibe (CI-1011), a synthetic ACAT inhibitor, has been reported to significantly reduce total triglycerides and VLDL-cholesterol levels without any changes in total cholesterol, LDL-cholesterol and HDL-cholesterol in patients with combined hyperlipidemia [37]. In addition, administration of avasimibe in combination with statins has been shown to enhance the lipid lowering effects of statins in patients with homozygous familial hypercholesterolemia [38].

Bile acid transport inhibitors

The failure of bile acid sequestrant cholestyramine and colestipol because of their non-specific nature of ion trapping and insignificant reduction in LDL-cholesterol has shifted the interest to develop bile acid transport inhibitors [39]. Specific ileal bile acid transport or apical Na⁺-dependent bile acid transport inhibitors that prevent the reabsorption of bile acid from lumen of small intestine to hepatic portal circulation have been recognized as novel lipid lowering agents. The decrease in hepatic bile acids with the resultant

increase in bile acid synthesis from cholesterol due to upregulation of 7- α -hydroxylase has been reported as a mechanism of action of bile acid transport inhibitors that subsequently lowers cholesterol levels [40]. Several compounds such as BRL 39924A, S-8921, R14 and 216U90 have been shown to reduce the levels of serum LDL-cholesterol with an increase in HDL-cholesterol in experimental animals [39]; however, their efficacy in humans needs to be determined.

Cholesterol ester transport protein (CETP) inhibitors

CETP facilitates the transport of cholesteryl esters from HDL to proatherogenic apolipoprotein B-containing lipoproteins including VLDL and LDL [41]. In various experimental studies, attenuation in CETP activity has resulted in an increase in the levels of HDL-cholesterol and a decrease in the levels of VLDL-cholesterol and LDL-cholesterol [41]. CETP inhibitors, JTT-705 and torcetrapib, have been shown to increase HDL-cholesterol in humans alone or in combination with statins [42–44]. Additionally, CETI-1, a vaccine that stimulates antibodies specific for CETP, is under development for potential use in reducing atherosclerosis [45]. On the other hand, these inhibitors appear to be ineffective in patients exhibiting higher level of triglycerides. Furthermore, the results are controversial in humans having mutations resulting in CETP inhibition [46]. Therefore, further clinical trials are needed to find the status of CETP inhibition in diverse groups of atherosclerotic patients

Lipoprotein(a) [Lp(a)] inhibitors

LP(a) is a lipoprotein comprised of apolipoprotein(a) [apo(a)] attached to the apolipoprotein B100 (apoB) of LDL. Lp(a) has been considered to possess both proatherogenic and prothrombotic properties by virtue of its similarity to LDL and apolipoprotein(a) to plasminogen. Elevated levels of Lp(a) are known to be associated with the development of atherosclerosis [47]. While Lp(a) has proven to be resistant to statin therapy it is not resistant to high doses of nicotinic acid [47], however the occurrence of flushing, itching, skin rashes, hepatotoxicity and increase in blood glucose levels has limited the use of nicotinic acid as an anti-atherosclerotic agent [34]. Recent evidence suggest

that inhibition of Lp(a) assembly *via* an initial non-covalent interaction between apoB100 and apo(a) after secretion of apo(a) from the liver and metabolism of VLDL to LDL in the circulation by apoB₄₃₇₂₋₄₃₉₂ peptide and its new variants may be a better choice for future therapy [48]. Other agents such as lipoprotein-associated phospholipase A₂ antagonist (SB-435495) [49], recombinant HDL apoA-I Milano/phospholipid complex particles (ETC-216) [50] and Liver-X-receptor ligands (T0901317 and GW3965) [51] are also currently under investigation to determine their efficacy in modifying cholesterol levels.

Renin-angiotensin system (RAS) blockade for the treatment of atherosclerosis

RAS comprises of a cascade of events starting with the activation of renin and conversion of angiotensinogen to inactive peptide angiotensin I (Ang I), which is further converted to active peptide Ang II by the angiotensin-converting enzyme (ACE). Ang II, the principle effector hormone of RAS, exhibits multiple effects through its action on Ang II type 1 (AT₁) receptors and plays an important role in the progression of atherosclerosis [52]. The deleterious effects of AngII are mainly mediated by its ability to cause vascular endothelial dysfunction, oxidation of LDL and enhancement of the interaction between OxLDL and macrophage scavenger receptor [53]. In addition, other mechanisms such as proliferation of vascular SMCs, induction of inflammatory responses by stimulating the release of platelet derived growth factor (PDGF), cytokines, chemokines as well as induction of extracellular matrix remodeling via activation of matrix metalloprotease are associated with the pro-atherosclerotic effects of Ang II [52, 53]. All these effects of Ang II are considered to be due to its ability to promote oxidative stress.

Angiotensin-converting enzyme (ACE) inhibitors

Various investigators have demonstrated that ACE inhibitors cause a significant reduction in the development of atherosclerosis in experimental animal models [54, 55]. Kowala *et al.* [56] have shown that

different ACE inhibitors have varying effects on specific stages of atherosclerosis as captopril mainly inhibits foam cell formation, whereas fosinopril reduces the plasma total LDL, VLDL and triglyceride cholesterol levels and the number of intimal macrophage-foam cells. It is pointed out that the anti-atherosclerotic effects of these ACE inhibitors were observed to be independent of their blood pressure lowering property [56]. Different experimental studies have shown that imidapril, a long acting ACE inhibitor, prevents the changes in G_i proteins and adenylate cyclase activity in MI [57], total cholesterol content of the descending thoracic aorta [58] and arteriosclerosis by inducing apoptosis in the cells with inflammatory lesions [59]. A newer sulfhydryl ACE inhibitor, zofenopril has been shown to cause reduction in oxidative stress and improvement in the NO pathway in patients with essential hypertension [60]. Another ACE inhibitor, ramipril, has been shown to cause a decrease in inflammation, which is manifested by reduction in the concentration of high-sensitivity C-reactive protein (hs-CRP) in patients with atherosclerosis [61] as well as chemokine expression by reduction of nuclear factor κ B (NF κ B) activation in human monocytes [62]. The protective effects of ramipril are associated with a reduction of mortality and end points of atherosclerosis such as MI and stroke; these are evidenced from the results of the HOPE (Heart Outcomes Prevention Evaluation) clinical trial [63]. Additionally, in the SECURE (Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E) clinical trial, which was a sub-study of HOPE, the occurrence and progression of atherosclerosis, was reported to be reduced by treatment with ramipril [64]. On the other hand, no significant benefit of ACE inhibitors, quinapril and enalapril, was observed in the QUITE (Quinapril Ischemic Events Trial) [65] and SCAT (Simvastatin/Enalapril Coronary Atherosclerosis Trial) clinical trials, respectively [66]. Differences in the methods of assessment of atherosclerotic plaque progression have been suggested as the reason for such a discrepancy [67].

AT₁ receptor antagonists

The anti-atherosclerotic effect of AT₁ receptor antagonists is linked to their higher affinity for AT₁ receptors with subsequent blockade of receptor-mediated pro-

atherosclerotic effects of Ang-II [68]. AT₁ receptor antagonists have been shown to cause a significant reduction in oxidative stress with an improvement in endothelial function [69, 70]. The improved endothelial function in response to AT₁ receptor antagonists has also been associated with increased availability of NO and is independent of the blood pressure lowering effect in atherosclerosis patients [71]. In addition, activation of LOX-1, lectin-like receptor for OxLDL, which is linked with endothelial dysfunction and monocyte adhesion as well as aggregation, has been shown to be inhibited by losartan in hypercholesterolemic rabbits [72]. In addition, the proliferation of SMCs manifested by the expression of early growth response gene c-fos and DNA synthesis in human vascular SMCs has been reported to be inhibited by losartan [73]. Direct effects of losartan on the reversal of early stages of atherosclerosis are associated with the reduction of intima-media thickness as observed in LVRS (Losartan Vascular Regression Study) [74]. Navalkar *et al.* [75] have demonstrated that a newer AT₁ receptor antagonist, irbesartan, decreases the inflammatory markers including vascular cell adhesion molecule-1 (VCAM-1), tumor necrosis factor- α (TNF- α) and superoxide anion in normotensive patients with stable CAD. Additionally, various clinical trials with AT₁ receptor blockers including Val-HeFT (Valsartan Heart Failure Trial) [76], VALIANT (Valsartan in Acute Myocardial Infarction) [77], RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study) [78], LIFE (Losartan Intervention For Endpoint reduction in hypertension study) [79] and CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity in patients with chronic heart failure) [80] have demonstrated that AT₁ receptor antagonists prevent different risk factors associated with the development of atherosclerosis and decrease the occurrence of cardiovascular events. AT₁ receptor antagonists mediated reduction of the expression of matrix metalloprotease (MMP)-8 and MMP-12 may be the reason for decrease in acute vascular events [81].

A large body of evidence has reported that combination of low doses of AT₁ receptor antagonists with low doses of statins act synergistically to attenuate neointima formation [82] as well as prevent oxidative stress in hypercholesterolemic patients [83]. Grote *et al.* [84] have suggested that blockade of AT₁ receptors may provide superior beneficial effects over ACE inhibitors because ACE inhibitors do not inhibit the production of Ang II from non-ACE generating systems such as chymase, cathepsin or tonin. Furthermore, AT₁ antagonists,

unlike ACE inhibitors, indirectly activate AT₂ receptors, which have anti-proliferative, pro-apoptotic and vasodilatory actions [85, 86]. On the other hand, additional beneficial effects of ACE inhibitors may be mediated by the accumulation of bradykinin [87]. However, Schieffer *et al.* [88] have demonstrated that AT₁ receptor blockade appears to exert stronger systemic anti-inflammatory and anti-aggregatory effects compared with ACE inhibition. On the basis of the available data, Nickenig [89] have suggested that a combination of statins with AT₁ receptor antagonists may be a better choice to prevent the development of CAD as well as to improve patient compliance. More information regarding the anti-atherosclerotic effect of AT₁ receptor antagonists and ACE inhibitors will be forthcoming after completion of the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study [90].

NO availability as a target for atherosclerosis treatment

Endothelium NO, a potent endogenous vasodilator, plays an important role in preventing the development of atherosclerosis. Prevention of leukocyte migration and adhesion to the vascular endothelium by a decrease in monocyte chemoattractant protein-1 (MCP-1) [91], surface adhesion molecules such as CD11/CD18, P selectin, VCAM-1 and ICAM-1 [92, 93] are the major mechanisms responsible for NO-induced protection in the early phases of atherosclerosis. Furthermore, NO prevents platelet aggregation and adhesion to the vascular wall [94] and inhibits the release of PDGFs, which are known to stimulate SMC proliferation [95]. The protection by NO in the latter stages of atherosclerosis is linked with the inhibition of DNA synthesis, mitogenesis, VSMC proliferation and migration [96]. A decrease in endothelial permeability, reduction in influx of LDL into the intima and inhibition of LDL oxidation [97] are other suggested mechanisms of the NO mediated prevention of atherosclerosis.

Although organic nitrates such as nitroglycerine, isosorbide mononitrate and isosorbide dinitrate are known NO donors used for the treatment of symptomatic CAD, the rapid development of tolerance during sustained therapy is the major limitation of their use [98]. Inactivation of NO by increased production of superoxide anions with subsequent formation of peroxynitrite and the depletion or oxidation of sulphydryl

groups (-SH) by large doses of these agents are the major mechanisms responsible for such an effect [98]. On the other hand, molsidomine, a direct NO donor, and its active metabolite, 3-morpholinodimethylamine-1 (SIN-1), do not cause tolerance because of thiol independent action [99]. However, SIN-1 has proatherosclerotic action as it causes the simultaneous production of NO and superoxide leading to the formation of peroxynitrite, which has cytotoxic effects through oxidation and nitration reactions [100, 101]. This was further supported by the ACCORD (Angioplastic Corvair Diltiazem) clinical trial as no improvement in clinical outcome of atherosclerosis such as nonfatal MI, coronary revascularization and death was observed after treatment with SIN-1 [102].

Recent studies have recognized S-nitrosothiols such as S-nitroso-N-acetylpenicillamine-1 (SNAP-1) as novel NO-donors, which are devoid of nitrate tolerance [103] and pro-oxidant properties [104]. Aizawa *et al.* [105] have reported that SNAP-1 exhibits potent anti-inflammatory property by a mechanism that involves the activation of protein kinase A *via* cGMP-dependent inhibition of phosphodiesterase 3 and subsequent decrease in TNF- α -induced-NF κ B-dependent adhesion molecule and chemokine expression. Another S-nitrosothiol, S-nitroso-glutathione (GSNO), has been demonstrated to be a potent inhibitor of platelet activation [106]. In addition, N-nitratopivaloyl-S-(N'-acetylalanyl)-cysteine ethylester (SPM 5185), a new compound containing a nitrate and a thiol moiety, has been shown to reduce intimal thickening and fatty streak formation in experimental animals [107]. Although the initial evidence of the effects of these newer NO donors seems to point to a protective role, large scale clinical trials are needed to establish these agents as potential anti-atherosclerotic treatments.

Ca²⁺ influx as a target for the treatment of atherosclerosis

Early atherosclerotic lesions are known to be associated with an increase in Ca²⁺ influx [108, 109]. Hypercholesterolemia has been recognized as an important factor in altering SMC permeability of Ca²⁺ by activating the voltage operated Ca²⁺ channels and thus significantly augments the intracellular Ca²⁺ concentration ([Ca²⁺]_i) in SMCs [110, 111]. The increase in SMC Ca²⁺ con-

centration has been reported to cause SMC proliferation and leads to atherosclerotic plaque progression [112]. However, the role of Ca²⁺ channel blockers in the treatment of atherosclerosis has not been clearly established because of the conflicting data, which have been obtained from clinical trials and animal studies [112]. It has been demonstrated that the anti-atherosclerotic effect of Ca²⁺ channel blockers is limited to the attenuation of the initial stages of atherosclerosis including fatty streak formation without having any effect on preexisting lesions [113]. The lack of lipophilicity and antioxidant effects are the major reasons for such discrepancies [114].

Recently, amlodipine, a third generation highly lipophilic L-type Ca²⁺ channel antagonist with antioxidant properties has been reported to prevent the development and progression of atherosclerosis in both experimental and clinical studies [115, 116]. Increase in the resistance of LDL to oxidative modification, prevention of SMC membrane remodeling, inhibition of SMC proliferation and migration, attenuation of TNF- α -induced endothelial apoptosis and modulation of vascular cell gene expression and extracellular matrix formation are the major mechanisms associated with the anti-atherosclerotic effect of amlodipine [114]. Moreover, clinically the anti-atherosclerotic effect of amlodipine in combination with statins is synergistic in nature [113]. This is important to note that the additive effect is not limited to new lesion formation but also inhibit the progression of established coronary atherosclerosis [113]. However, the protective effect of amlodipine, unlike irbesartan, on development of diabetes-induced plaque formation in apoprotein E-null was not observed [117]. Azelenidine, a newly developed long-acting Ca²⁺ channel antagonist with antioxidant property, which inhibits TNF- α -induced interleukin-8 expression in endothelial cells, may be a better choice in hypertensive patients with metabolic syndrome [118, 119].

Oxidative stress as a target for atherosclerosis treatment

Oxidative stress, characterized by lipid and protein oxidation in the vascular wall, has been shown to

Fig. 3 Involvement of oxidative stress in the development of atherosclerotic plaque. LDL: low density lipoprotein; HDL: high density lipoprotein; ↑: increase

play a central role in the development of atherosclerosis [120]; this is shown in Fig. 3. The alteration in endothelial permeability due to endothelial injury causes transmigration of LDL particles into the intima, where these are modified by oxidative stress to OxLDL [121]. OxLDL is a potent chemoattractant for monocytes and T lymphocytes and promotes the differentiation of monocytes to tissue macrophages. OxLDL further induces the expression of macrophage scavenger receptor and thus promotes the foam cell formation [120, 121]. The uptake of OxLDL by macrophages is the major stimulant for the release of various cytokines and initiates an inflammatory response in the initial stages of atherosclerosis [11]. In addition, OxLDL is an important mediator to cause plaque instability mainly by activating matrix metalloproteases [122].

Supplementation with Vitamin E (α -tocopherol, α -TOH), the major lipid soluble antioxidant in LDL, has been reported to prevent the progression of atherosclerosis under various experimental conditions; however the results of the randomized controlled clinical trials are controversial [123]. It has been demonstrated that pro-oxidant activity of α -TOH *via* formation of α -tropheroxyl radical (α -TO $\cdot$) leading to the production of lipid hydroperoxides in lipoproteins may be the reason for failure of vitamin E as an anti-atherosclerotic agent [124]. Recently the results

of ASAP (Antioxidant Supplementation in Atherosclerosis Prevention) have reported that long term supplementation of vitamin E with slow-release vitamin C decreases the progression of carotid atherosclerosis in hypercholesterolemic humans [125]. Vitamin C-induced reduction of α -TO $\cdot$ to α -TOH has been suggested as the reason for the protective effect of combination in ASAP study [125]. However, it is important to note that protection with the combination of vitamins was limited only to men as no protection was observed in women. Lower baseline levels of antioxidants in men than women may, in part, be responsible for such differences between genders [125].

Another antioxidant, probucol, has been reported to prevent the oxidative modification of LDL [126]. ProbucoL also prevents the coronary restenosis after balloon angioplasty and regression of carotid atherosclerosis as observed in MVP (MultiVitamins and ProbucoL) and FAST (Fukuoka Atherosclerosis Trial) studies, respectively [127]. On the other hand, animal studies related with the anti-atherosclerotic property of probucoL have yielded conflicting data. In rabbits it has been shown to prevent the development of atherosclerosis [126], whereas in apolipoprotein E-deficient mice probucoL treatment was observed to result in an increase in lesion severity [128]. It is important to note that one limitation of α -TOH is that

it is unable to exert its antioxidant effects in the core of LDL whereas probucol is active at this site. However, the prolongation of the QT interval and reduction in HDL levels in patients treated with probucol remains a long-term safety concern and thus the anti-atherogenic benefit of this antioxidant is questionable [127, 129]. A new antioxidant, BO-653, has been designed based on the chemical structures of probucol and Vitamin E with the aim to retain advantages and overcome the limitations of these antioxidants [130]. BO-653 has higher antioxidant activity than Vitamin E and probucol, which is related to the stability of its radical and higher lipophilicity [131]. Furthermore, BO-653 has shown its superiority over probucol as an anti-atherosclerotic agent as it did not lower HDL levels [129, 132]. Although Yamauchi *et al.* [133] have reported that administration of BO-653 to healthy human subjects causes the protection of lipids in the plasma from oxidation, clinical trials in atherosclerotic patients need to be conducted to determine the potential of BO-653 as an anti-atherosclerotic agent.

Polyphenolic compounds in red wine have been reported to interfere with the molecular processes underlying the initiation, progression, and rupture of atherosclerotic plaques in different experimental studies [134, 135]. While statins (pravastatin, simvastatin and atorvastatin), fibrates (bezafibrate and fenofibrate), β -adrenoceptor blockers (carvedilol), ACE inhibitors (captopril) and Ca^{2+} channel antagonists (lacidipine) have been demonstrated to exhibit antioxidant activities [136], the importance of this biological effect in retarding the atherogenic process is not completely understood.

Vascular inflammation as a target for atherosclerosis treatment

The complex interaction between pro-inflammatory cytokines such as TNF- α and IL-1 β , hs-CRP, OxLDL and CD40/CD40 ligand upon endothelial dysfunction increases the expression of inflammatory mediators (VCAM-1, ICAM-1 and selectin) [11, 137]. This process promotes the adhesion of monocytes to endothelial surface and their migration to arterial intima. Once in the arterial intima, monocytes develop into macrophages and convert to foam cells by internalizing OxLDL. The foam

cells further secrete pro-inflammatory cytokines, which aggravate the process of atherosclerosis plaque formation [138]. In addition, T-cells migrate to the intima and further increase the inflammatory process by stimulating the release of pro-inflammatory cytokines including interferon- γ [137]. Newer therapeutic agents with lipid modifying, antioxidant and anti-inflammatory properties have been recognized as composite vascular protectants (v-protectants) [139]. Composite v-protectants are small molecular compounds with dual properties, combining protection of the arterial lining and LDL cholesterol lowering [139].

The lead clinical development compound of this category is AGI-1067, which is a monosuccinic acid ester of probucol [127, 139]. It exhibits lipid lowering and strong antioxidant properties, equipotent to those of probucol [139]. In addition, AGI-1067 has anti-inflammatory properties as it inhibits the inducible expression of the redox-sensitive genes such as VCAM-1 and MCP-1, in endothelial cells as well as TNF- α , IL-1 β , and IL-6 production in peripheral blood mononuclear cells [140]. Furthermore, TNF- α -induced expression of VCAM-1, MCP-1 and E-selectin in human aortic endothelial cells has been shown to be inhibited by AGI-1067 [141]. In the Canadian Antioxidant Restenosis-1 (CART-1) Trial, AGI-1067 has exhibited a direct anti-atherosclerotic effect by improving the luminal dimensions of reference segments in the percutaneous coronary vessels [142]. Two important on going trials, CART-2 and ARISE (Aggressive Reduction of Inflammation Stops Event), will test the antioxidant and anti-inflammatory effects of AGI-1067 in the reduction of both atherosclerosis progression in non-percutaneous coronary vessels and post-percutaneous coronary restenosis as well as on the outcome measures such as death due to coronary disease, MI, stroke, coronary re-vascularization and unstable angina in patients with CAD, respectively [143]. Another new agent, S17834, has been reported to inhibit the generation of superoxide anion as well as the early stages of TNF- α -induced activation of gene and protein expression of endothelial VCAM-1, ICAM-1, and E-selectin in human umbilical vein endothelial cells [144]. Potential clinical applications of such agents as vascular protectants for the treatment of atherosclerosis need further investigation.

Fig. 4 Platelet activation-mediated alterations leading to the development of atherosclerotic plaque and thrombus formation. PDGF; platelet derived growth factor; LPA: lysophosphatidic acid; LDL: low density lipoprotein; 5-HT; 5-hydroxytryptamine; HDL: high density lipoprotein SMC: smooth muscle cell; ↑: increase.

Preliminary studies have shown that infectious agents such as influenza play an important role in the development of atherosclerosis by initiating a chronic vascular or systemic inflammatory process [145]. Emerging evidence has suggested that influenza vaccination in combination with standard lipid lowering therapy reduce the risk of death and ischemic events in patients suffering from MI and post-angioplasty [146]. However, further studies are needed to establish the antiatherosclerotic potential and cost-effectiveness of influenza vaccination in patients with different risk factors.

Inhibition of platelet activation for atherosclerosis treatment

It is well recognized that platelet activation plays an important role in the development of atherosclerotic plaque as well as in thrombotic vascular occlusion at the site of ruptured coronary atherosclerotic plaque [147] (Fig. 4). The rupturing of the plaque exposes subendothelial collagen, tissue factor and von Willebrand factor to circulating blood and triggers the cascade of platelet-mediated processes [148]. Receptor mediated activated platelet adhesion to the ruptured microvascular surface and embolization of platelet aggregants are the predominant mechanisms leading to the impairment of coronary microcirculation [148].

Inhibitors of prostaglandin (PG)-induced platelet activation

Activated platelets increase the formation of arachidonic acid from plasma membrane phospholipids by an increase in the activity of phospholipase A_2 . Cyclooxygenase-1 (COX-1) enhances the metabolism of arachidonic acid to PGG_2 , which is further converted to PGH_2 by the enzyme peroxidase. Activation of thromboxane (TXA_2) synthase converts PGH_2 to TXA_2 in the platelets. The released TXA_2 from platelets causes an increase in $[Ca^{2+}]_i$ by acting on its receptors and sets a positive feed back loop for the generation of additional TXA_2 . This action enhances the platelet aggregation as well their recruitment to the injury site [149]. Aspirin, a non-steroidal anti-inflammatory drug inhibits COX-1 and prevents PG synthesis [150, 151]. Several primary prevention trials such as Hypertension Optimal Treatment Trial, Thrombosis Prevention Trial, Primary Prevention Project and Physicians Health Study have revealed a significant reduction in the incidence of acute MI after aspirin treatment [152]. Similarly, in secondary prevention trials, long term treatment with aspirin decreases the incidence of non-fatal ischemic stroke, non-fatal acute MI and death in patients with a previous history of MI, unstable angina and stroke [152, 153]. Despite these beneficial effects, the resistance to aspirin develops in 5–25% of patients

with ischemic heart disease as these patients experience recurrent arterial thrombotic events during long-term aspirin therapy [152]. Non-atherothrombotic causes of vascular disease, requirement of higher doses of aspirin, poor patient compliance, alternative pathways of platelet activation, and aspirin-insensitive TXA₂ biosynthesis have been proposed as mechanisms responsible for the apparent failure of aspirin as an anti-thrombotic agent [154]. In addition, hypercholesterolemia, genetic polymorphism of glycoprotein (GP) IIb/IIIa receptor resulting in allelic variant P1A² and increased platelet turnover rate have been linked to aspirin resistance [154, 155].

A new TXA₂ synthase inhibitor, camonagrel, has been shown to be protective in cats with extracorporeal thrombogenesis and patients with peripheral atherosclerosis. Conversion of PG peroxides from TXA₂ to prostacyclin (PGI₂), without having any effect on cyclic-GMP levels, has been reported as the mechanism of such an effect [156]. However, some caution should be exercised while administering camonagrel with aspirin because both TXA₂ and COX-1 inhibitors have antagonistic effects [156]. While TXA₂ receptor antagonists may be a better choice [157], this still needs to be confirmed.

GP IIb/IIIa receptor antagonists

The activation of platelets initiates "inside-out" signaling, which causes conformational change in the surface adhesion receptor, integrin α IIb β 3 (GP IIb/IIIa receptor). This alteration in the receptor increases its affinity for the adhesive protein fibrinogen; the binding of receptor with fibrinogen causes an "outside-in" change in GP IIb/IIIa receptor, which transmits the receptor mediated intraplatelet signals resulting in platelet aggregation and platelet plug formation [158]. Due to the potential role of GP IIb/IIIa receptors in platelet aggregation, their antagonists have been recognized as antithrombotic agents [159, 160]. Three major clinical trials, EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications) [161], EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) [162] and CAPTURE (c7E3 Fab antiplatelet therapy in unstable refractory angina) [163] have reported the efficacy of

intravenous GP IIb/IIIa receptor antagonist, abciximab (c7E3), in reducing acute coronary events in patients after angioplasty, coronary artery stenting and refractory unstable angina, respectively. In addition, long-term follow-up of EPIC and EPISTENT trials have reported that abciximab treatment prevented all cause mortality after percutaneous coronary revascularization [164]. However, induction of thrombocytopenia by abciximab in a small population of patients in the above mentioned trials halted its use for future therapy [165]. An intravenous non-peptide GP IIb/IIIa antagonist, tirofiban, has also been shown to prevent the early events in patients, but it has no effect on long-term survival [166]. In addition, oral GP IIb/IIIa receptor antagonists have failed to demonstrate any reduction in long-term ischemic events [167]. Therefore, the current use of GP IIb/IIIa receptor antagonists is limited to certain specific conditions because abciximab is a preferred agent to prevent the complications of percutaneous coronary interventions [168] and tirofiban is a recommended drug in high risk patients with elevated levels of troponin or diabetes mellitus [160].

ADP receptor antagonists

ADP binding to purinergic P2Y receptors is known to cause platelet aggregation and platelet shape change, which subsequently increases the activation of GP IIb/IIIa receptor [169]. Thioenopyridine derivatives, clopidogrel and ticlopidine, have been proven to be useful in preventing atherothrombotic events in cardiovascular, cerebrovascular and peripheral vascular diseases [170]. It is pointed out that clopidogrel is more potent, has rapid onset of action and lower incidence of side effects such as neutropenia and thrombocytopenia as compared to ticlopidine [171]. Clopidogrel has also been shown to be more beneficial than aspirin in terms of lowering the combined risk of MI, ischemic stroke and vascular death as observed in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) clinical trial [172]. However, the combination of aspirin with clopidogrel is beneficial for ischemic stroke in experiment animals and after acute MI in patients [173]. Similar beneficial

effects of aspirin-clopidogrel combination has also been reported to prevent not only the subacute stent thrombosis in patients subjected to percutaneous coronary interventions [174], but also adverse cardiovascular events in patients with non-ST segment elevation associated with acute coronary syndrome [175]. It should be mentioned that statins do not affect the ability of clopidogrel to inhibit platelet function in patients undergoing coronary stenting as observed in the INTERACT (Interactions of Atorvastatin and Clopidogrel Therapy) trial [176]. However, the effects of clopidogrel are not uniform in all patients because clopidogrel resistance has been reported in 4-30% of patients treated with conventional doses [177]. Further experimental and clinical studies are needed to find the mechanisms, which are related to the individual variation of such an effect.

5-HT_{2A} receptor antagonists

5-HT, secreted from activated platelets, directly accelerates platelet aggregation and potentiates the response of platelets to other agonists such as adenosine diphosphate, collagen, and TXA₂. 5-HT also promotes the proliferation and migration of SMCs and is considered to play an important role in the development and progression of atherosclerosis [178, 179]. The 5-HT_{2A} receptor antagonist, sarpogrelate (MCI-9042), has been shown to inhibit 5-HT mediated platelet aggregation and SMC proliferation as well as increase in [Ca²⁺]_i [180–182]. Anti-atherosclerotic effect of sarpogrelate in experimental animals is associated with stabilization of vulnerable plaque due to a reduction in the degradation of the extracellular matrix as a result of decreased expression of MMP-1 and MMP-2 [183]. In addition, the beneficial action of sarpogrelate has been linked to an increase in the expression of endothelial NOS [183]. It is pointed out that the anti-atherosclerotic effect of sarpogrelate is potentiated by vitamin E, a known antioxidant [183]. Recent clinical trials have reported that sarpogrelate treatment improves the coronary microcirculation in patients with CAD [184] and reduces restenosis after coronary stenting [185].

Lysophosphatidic acid (LPA), a water-soluble phospholipid, released from activated platelets

and oxLDL has also been reported to cause platelet aggregation and VSMC proliferation, which is associated with an increase in [Ca²⁺]_i under experimental conditions [186–188]. Although from these experimental studies LPA has been identified as an important mediator of atherosclerogenesis and thrombogenesis, future research is needed to determine the benefits of experimental therapies targeting to block the LPA receptors and associated signal transduction processes. Recent studies have demonstrated that casein kinase II (CK2) plays a significant role in LPA-mediated VSMC proliferation [188] and scar formation post-MI [189], thus CK2 inhibitors seem to be potential antiatherosclerotic agents for future therapy. In addition, a variety of other targets such as blockade of serotonin reuptake, protease activated receptor and leptin receptor [167] has been recognized as potential targets for effective anti-platelet agents that can be used alone or as adjuncts with optimal doses of available regimens.

SMC proliferation as a target for treatment of atherosclerosis

The inflammatory mediators released from monocytes promote the proliferation and migration of SMCs from media to intima. Once in the intima, SMCs cause the production of cytokines, growth factors and extracellular matrix consisting of collagen and proteoglycans, and thus in turn contribute to atheroma growth and formation of the fibrous cap and consequent stabilization of the plaque [190]. However, rupture of the plaque leads to acute occlusion due to thrombus formation, resulting in MI or stroke at advanced stages of atherosclerosis [190]. Excessive cell proliferation and migration are also involved in the growth of vascular obstructive lesions as a consequence of procedures used to treat atherosclerosis. These complications include restenosis after balloon angioplasty, transplant vasculopathy, and graft atherosclerosis [191].

Rapamycin, a macrolide antibiotic and immunosuppressant, inhibits VSMC proliferation by binding to FK506 protein (FKBP12). It blocks the cell cycle progression at G1/S phase [192], which is

Table 2 Possible targets for drug therapy of atherosclerosis

Target of action	Drug category	Therapeutic effects
Cholesterol levels	HMG-CoA reductase inhibitors Cholesterol absorption inhibitors PPAR- α activators ACAT inhibitors Bile acid transport inhibitors CETP inhibitors Lipoprotein (a) inhibitors	↓ LDL cholesterol [17–30] ↓ LDL cholesterol, ↑ HDL cholesterol [31–34] ↓ Triglycerides, ↑ HDL cholesterol [5, 35] ↓ Triglycerides, ↓ VLDL cholesterol [36] ↑ 7- α -hydroxylase [39] ↑ HDL cholesterol [42–46] ↓ Lp (a) assembly [47–51]
Endothelial dysfunction	NO donors ACE inhibitors AT ₁ receptor blockers	↑ NO, ↓ MCP-1, ↓ CD11/CD18, ↓ P selectin, ↓ VCAM-1, ↓ ICAM-1 [98–107] ↓ LDL, ↓ VLDL, ↓ triglycerides, ↓ oxidative stress, ↓ hs-CRP [56–66] ↑ NO, ↓ Inflammatory markers [68–88]
Ca²⁺ influx	Ca ²⁺ channel blockers	↓ Ca ²⁺ -overload, ↓ oxidative stress, ↓ SMC remodeling [108–119]
Oxidative stress	Antioxidants	↓ LDL oxidation [123–136]
Vascular inflammation	Anti-inflammatory agents	↓ VCAM-1, ↓ MCP-1, ↓ TNF- α , ↓ IL- β 1, ↓ IL-6 [137–144]
Platelet aggregation	PG-induced platelet activation inhibitors GP IIb/IIIa receptor antagonists ADP receptor antagonists 5-HT _{2A} receptor antagonists	↓ PG synthesis [149–156] ↓ Affinity of fibrinogen to GP IIb/IIIa receptor [158–168] ↓ ADP binding to purinergic P2Y receptors [169–177] ↓ 5-HT mediated platelet aggregation, ↓ SMC proliferation [178–185]
SMC proliferation	Growth inhibitors	↓ Cell cycle progression [190–199]

HMG-CoA: 3-hydroxy-3-methyl glutaryl Coenzyme A; LDL: low-density lipoprotein; HDL: high-density lipoprotein; VLDL: very low-density lipoprotein; PPAR- α : peroxisome proliferative activator receptor- α ; ACAT: acyl-cholesterol acyl transferase; CETP: cholesterol ester transport protein; NO: nitric oxide; MCP-1: monocyte chemoattractant protein-1; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule; ACE: angiotensin converting enzyme inhibitors; AT₁: angiotensin II type 1; hs-CRP: high-sensitivity C-reactive protein; TNF- α : tumor necrosis factor- α ; IL: interleukin; PG: prostaglandin; SMC: smooth muscle cell; 5-HT: 5-hydroxytryptamine

also associated with a marked suppression of IL-2 and IL-4 mediated cell proliferation and cell migration [193]. Experimental studies and preliminary clinical investigations have demonstrated that rapamycin coated stents prevent neointimal hyperplasia and restenosis [194]. ABT-578, a new synthetic analog of rapamycin, designed to inhibit smooth muscle cell proliferation, by blocking the function of the mTOR cell cycle regulatory protein

is also under clinical trials [195]. Furthermore, an anticancer agent, paclitaxel (taxol), has been shown to inhibit G2/M phase of the cell cycle and attenuates proliferation and migration of SMCs in a dose-dependent manner in monocultures and co-cultures in the presence of mitogens such as PDGF, basic fibroblast growth factor (bFGF) and thrombin [196]. In addition, paclitaxel has been shown to reduce neointima formation in rabbits after balloon

angioplasty [196]. Furthermore, the beneficial effects of paclitaxel prevention of restenosis have been recognized in different clinical trials [195]. Recent studies have found that this agent can exert a highly supra-additive antiproliferative effect in combination with an immunosuppressant agent, cyclosporine A, due to cell cycle arrest at G2/M transition [197]. A newer PDGF receptor kinase inhibitor, AGL 2043, which arrests cell growth at the G0/G1 phase of the cell cycle has also been shown to inhibit balloon injury in experimental animals [198]. However, further studies are needed to determine the long-term drug toxicity as well as late vascular and systemic effects of these inhibitors. Recently Dzau *et al.* [199] have suggested the potential benefits of antisense oligonucleotides in cell cycle inhibition leading to prevention of SMC proliferation. It is important to note that antiproliferative therapy can only be used for the treatment of conditions associated with the management of atherosclerosis rather than for the initial stages of the disease, as these agents can increase the susceptibility of the plaque to rupture and thus cause an increase in acute ischemic events [199].

Conclusions

A growing body of evidence has suggested that in addition to inhibition of cholesterol biosynthesis, drugs targeted to block the absorption of dietary cholesterol, increase HDL-cholesterol, lower LDL-cholesterol and decrease triglyceride levels have been found to be effective in the treatment of atherosclerosis. However, it is emphasized that the beneficial effects of the currently used lipid-lowering agents are partial in nature and the aggressive therapy with high doses of these interventions invariably produce adverse actions. Furthermore, pharmacological blockade of RAS, Ca²⁺ influx, SMC migration and proliferation, oxidation of LDL and activation of platelets have been demonstrated to be protective in patients at different stages of atherosclerotic development. Identification of the involvement of inflammatory processes in atherosclerosis has also opened the access to a wide variety of anti-inflammatory agents for the treatment of disease. Table 2 summarizes the different pharmacological targets and the major therapeutic effects of various drugs for the

treatment of atherosclerosis. Although newer compounds with greater protective effects than the currently used therapies have been introduced, the implementation of these compounds for future therapy needs detailed clinical investigation. In fact, a combination therapy with these agents needs to be designed for improving the treatment of atherosclerosis. Since atherosclerosis is multifactorial in nature and develops decades earlier than its clinical manifestation, extensive studies are required to produce drugs to overcome the individual patient variation. In addition, development of agents for patients with genetic polymorphism in lipid metabolism or infectious basis of the disease needs to be investigated. Although novel therapies of atherosclerosis are considered to have great promise for treatment of the disease, it should be noted that none of these drugs are devoid of side effects. Thus a more stringent approach should be practiced to assess the benefits in terms of side effects of each therapy. Since, several clinical trials have been sponsored by pharmaceutical industries, it is important to exercise some caution from scientific view point for avoiding any biased conclusion while evaluating the clinical outcome of each trial.

Acknowledgements

The work reported in the article was supported by a grant from the Canadian Institutes of Health Research. HKS is a predoctoral fellow of the Heart and Stroke Foundation of Canada and recipient of the Government of Manitoba Graduate Student Award.

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