Review Article

Stabilization of high-risk plaques

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Abstract: The prevalence of atherosclerotic cardiovascular diseases (ASCVDs) is increasing globally and they have become the leading cause of death in most countries. Numerous experimental and clinical studies have been conducted to identify major risk factors and effective control strategies for ASCVDs. The development of imaging modalities with the ability to determine the plaque composition enables us to further identify high-risk plaque and evaluate the effectiveness of different treatment strategies. While intensive lipid-lowering by statins can stabilize or even regress plaque by various mechanisms, such as the reduction of lipid accumulation in a necrotic lipid core, the reduction of inflammation, and improvement of endothelial function, there are still considerable residual risks that need to be understood. We reviewed important findings regarding plaque vulnerability and some encouraging emerging approaches for plaque stabilization.

Keywords: Atherosclerotic cardiovascular diseases (ASCVDs); inflammation; low-density lipoprotein cholesterol (LDL-C); statins; thin-cap fibroatheroma (TCFA)

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Introduction

According to the World Health Organization (WHO), an estimated 17.5 million people died from atherosclerotic cardiovascular diseases (ASCVDs) in 2012, which represents 31% of all global deaths. Various risk factors are associated with the increased rate of adverse events and the increased mortality of ASCVDs (1). It has been proven that maintaining a healthy lifestyle, such as by not smoking, maintaining a healthy body mass index, exercise, and a healthy diet, is important for preventing ASCVDs (2). However, people develop numerous risk factors, such as dyslipidemia, diabetes, and hypertension, which contribute to the atherosclerotic plaque burden and lead to ASCVDs. Medical treatments that target ASCVD risk factors have been proven to reduce adverse events and mortality (3).

With respect to reducing mortality, it is especially important to elucidate the mechanisms of atherosclerotic plaque development and to identify approaches to stabilize atherosclerotic plaque, especially "vulnerable plaque".

Pathology of "vulnerable plaque"

It is difficult to distinguish vulnerable plaque from atherosclerotic lesions in a clinical setting, and this has led to the development of imaging modalities that can detect high-risk atherosclerotic plaques (4). Although coronary angioscopy was developed in the 1980's (5), a morphological approach is insufficient to capture the detailed mechanisms of plaque vulnerability. Therefore, other imaging modalities with the ability to clarify the characteristics of plaque composition have been developed, such as intravascular ultrasound-virtual histology (IVUS-VH), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS).

These imaging modalities and pathological studies

have demonstrated that acute myocardial infarction (AMI) can be caused by the rupture or erosion of a coronary atherosclerotic plaque (6,7). Atherosclerotic plaque consists of various components, i.e., lipid, calcified lesion, vascular smooth muscle cells (VSMCs), and inflammatory cells (i.e., T lymphocytes and macrophage cells). While the concept of atherosclerosis is complicated, it has been recognized that the stability of atherosclerotic plaque depends on the relationships among these components. VSMCs synthesize collagen I and III, which are important for plaque stabilization. On the other hand, inflammatory cells release various molecules, including metalloproteinases (MMPs), which lead to plaque instability.

Morphological and pathological studies have demonstrated that infiltrated inflammatory cells and the percentage of the lipid core are associated with positive remodeling (PR), which reflects the vulnerability of a culprit lesion (8). Fibrous-cap atheroma can be divided into a coronary arterial lumen and a lipid or necrotic core, and its thickness reflects plaque stability. Thin-cap fibroatheroma (TCFA), which is a morphological feature of vulnerable plaque, i.e., rupture-prone plaque, is characterized by a large lipid or necrotic core with an overlying fibrous cap measuring <65 μm, consisting of rare VSMCs, PR, spotty calcification, and numerous inflammatory cells (9-11). Both the size of the necrotic core and the thickness of TCFA may be structural determinants of vulnerability (12).

Vulnerable plaques by erosion (erosion-prone plaques), which lack surface endothelium, are defined solely by their associated events. Coronary plaque erosion accounts for 40% of thrombotic coronary sudden deaths (13), and is common in smokers and younger patients, especially premenopausal women (14). VSMCs and proteoglycans are predominant, while inflammatory cells are variable (13-15). The missing endothelium may be associated with vasospasm, and the vessels show negative remodeling (14,15). While the mechanisms of erosion are clearly different from those of plaque rupture, we do not yet know the details.

Targets for plaque stabilization

LDL cholesterol and cardiovascular events

It is well known that lowering the low-density lipoprotein cholesterol (LDL-C) level is useful in both the primary and secondary prevention of cardiovascular events (16-18). Statins are the most common therapeutic agents for lipid-lowering (19). The major effect of statins is the reduction of LDL-C levels through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins have favorable pleiotropic effects on atherosclerosis, including a reduction in lipid volume, anti-inflammatory activity, and improvement of endothelial function (20-22). They are now considered to be essential for treating ASCVDs due to their impact on atherosclerotic plaque. The classical understanding is that the infiltration of LDL-C to the intima is an early step that induces subsequent inflammatory responses in the vessel wall. Statins exert pleiotropic effects to interrupt inflammation within atherosclerotic plaque, which suppresses the secretion of inflammatory mediators (23).

A meta-analysis in 14 randomized clinical trials (RCTs) reported a relationship between achieved LDL-C and major adverse cardiac events (MACE) (24). In this study, there was a 12% proportional reduction in all-cause mortality per 1.0 mmol/L (39 mg/dL) reduction in LDL-C [rate ratio (RR) 0.88; 95% CI, 0.84–0.91], and corresponding reductions in myocardial infarction or coronary death (RR 0.77; 95% CI, 0.74–0.80), in the need for coronary revascularization (RR 0.76; 95% CI, 0.73–0.80), and in fatal or non-fatal stroke (RR 0.83; 95% CI, 0.78–0.88). The Collaborative Atorvastatin Diabetes (CARDS) study assessed the effectiveness of statin (atorvastatin 10 mg) therapy for the primary prevention of major cardiovascular events in patients with diabetes mellitus (DM) without high concentrations of LDL-cholesterol. The group allocated to statin was associated with a 37% reduction in the incidence of major cardiovascular events (P=0.001) compared to the placebo group. Acute coronary heart disease events were reduced by 36%, coronary revascularization by 31%, and stroke by 48% (25). Diabetic patients have a high atherosclerotic risk with about a three-fold increased risk of cardiovascular disease (26). This study suggested that statins are also potent in type 2 diabetes even without high concentrations of LDL-cholesterol. The PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) study showed that an achieved LDL-C under 60 mg/dL was associated with a lower risk of MACE in patients after acute coronary syndrome (ACS). (27) In this study, patients with ACS who were treated with atorvastatin were divided into 5 groups according to four-month LDL-C levels: >100, >80 to 100, >60 to 80, >40 to 60, and <40 mg/dL. Both of the lowest LDL groups, >40 to 60 (hazard ratio 0.68; 95% CI, 0.50–0.92) and <40 (hazard ratio 0.61; 95% CI, 0.40–0.91),

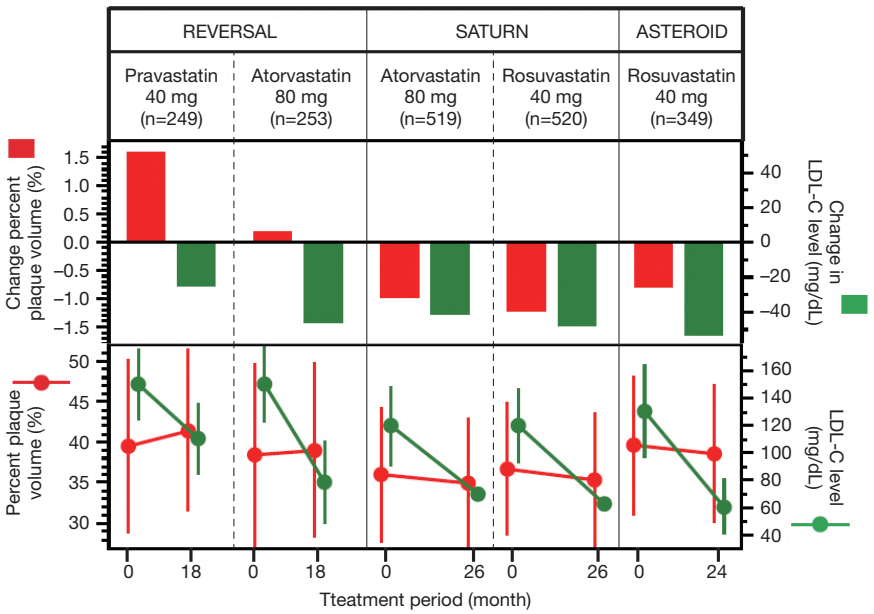

Figure 1 IVUS studies examining the impact of statin therapy on plaque progression/regression. The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) (32) study compared the efficacy of two statin regiments of different lipid lowering intensities on coronary atherosclerosis. The SATURN (34) (Effect of Rosuvastatin versus Atorvastatin) study compared the efficacy of two intensive statin regiments on coronary atherosclerosis. The ASTEROID (28) (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) study was the first large-scale IVUS study to evaluate the effect of intensive statin therapy on coronary atherosclerosis. LDL-C, low-density lipoprotein cholesterol; IVUS, intravascular ultrasound.

showed significantly lower endpoint rates than the reference group (>80 to 100).

Reduction of LDL cholesterol and modification of plaque instability

Various imaging modalities have been used to elucidate the mechanism underlying these relationships, and have demonstrated that statin therapies attenuate plaque progression and strengthen plaque stability. Various studies using IVUS have demonstrated that lipid-lowering therapy with statins can achieve plaque regression (28). The ESTABLISH (Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis During Half a Year After Coronary Event) study clarified for the first time that statin (atorvastatin 20 mg daily) significantly reduced plaque volume consistent with a reduction in the LDL-C level (29). The PROSPECT (30) (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) and VIVA (31) (VH-IVUS in vulnerable atherosclerosis) studies showed that the coronary plaque burden was closely related to MACE risk. Furthermore, the optimal level of LDL-C has been sought, i.e., high-intensity statin therapy (HIST) *vs.* low-intensity statin treatment (LIST) (28,32,33). In the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study, patients were randomly assigned to receive a moderate lipid-lowering regimen (40 mg of pravastatin) or an intensive lipid-lowering regimen (80 mg of atorvastatin) for 18 months. The primary efficacy parameter was the percentage change in atheroma volume as analyzed by IVUS. Although the coronary atherosclerosis progressed in the pravastatin group, progression did not occur in the atorvastatin group. As a result, the progression rate was significantly lower in the atorvastatin (intensive) group, which suggested that HIST is superior to LIST for slowing plaque progression (*Figure 1*).

A lot of studies have reported that statin therapies have favorable effects on the coronary plaque composition. Some studies used coronary angioscopy, with which the lipid core can be seen through TCFA, but not through a thicker fibrous cap. Takano *et al.* first reported in 2003 using angioscopy that the administration of atorvastatin for 12 months improved the yellow grade of coronary plaques,

which is associated with vulnerability to disruption. There was a strong correlation between the changes in LDL-C levels and the changes in the mean yellow score (r=0.81, P<0.0001) (35). Recently, color fluorescent angioscopy has become available as an advanced modality. It can be used to visualize not only collagen fibers but also oxidized LDL, and can provide useful information related to the plaque composition (36).

Among the reports with IVUS, Taguchi *et al*. reported that early statin therapy reduced the necrotic core component in patients with ACS, even in the case of plaque progression (37). A study with rosuvastatin (low dose: 5 mg/day, high dose: 40 mg/day) in patients with ST-segment elevation myocardial infarction (STEMI) clarified that the necrotic core component was reduced only in the high-dose rosuvastatin group (low dose; baseline 44.6±38.2 mm^3, 12-month follow-up 41.2±40.3 mm^3, P<0.29 *vs*. high dose; baseline 47.4±38.2 mm^3, 12-month follow-up 40.7±34.4 mm^3, P=0.003) (38). Another study that used VH-IVUS in patients with stable angina pectoris (AP) demonstrated that one year of lipid-lowering therapy with fluvastatin reduced the fibro-fatty volume (baseline 80.1±57.9 mm^3 *vs*. follow-up 32.5±27.7 mm^3, P<0.0001) and increased the fibrous tissue volume (baseline 146.5±85.6 mm^3 *vs*. follow-up 163.3±94.5 mm^3, P<0.0001). In addition, this study showed a positive correlation between the changes in LDL-C levels and the changes in the fibro-fatty volume (R=0.703, P<0.0001) (39). The TRUTH (Treatment With Statin on Atheroma Regression Evaluated by Intravascular Ultrasound With Virtual Histology) study also demonstrated that statin therapies in patients with stable and unstable AP not only reduced the fibro-fatty volume at 8 months (pitavastatin 4 mg/day; baseline 1.09 mm^3/mm, follow-up 0.81 mm^3/mm, P=0.001, pravastatin 20 mg/day; baseline 1.05 mm^3/mm, follow-up 0.83 mm^3/mm, P=0.0008) but also increased the calcium volume (pitavastatin 4 mg/day; baseline 0.42 mm^3/mm, follow-up 0.55 mm^3/mm, P=0.001, pravastatin 20 mg/day; baseline 0.44 mm^3/mm, follow-up 0.55 mm^3/mm, P=0.005) (40). Recently, a post-hoc analysis of 8 prospective randomized trials using IVUS revealed that statins promote calcification in coronary plaques, and the changes in the formation of calcification were independent of LDL-C and CRP (41). These effects of statins on coronary calcification may reduce the vulnerability of coronary plaques.

Some studies using OCT demonstrated that the fibrous-cap tended to thicken in response to HIST (42,43). In addition, the increase in fibrous cap thickness achieved with a HIST was significantly correlated with the reduction of infiltrated macrophages, LDL-C, oxidized LDL, high-sensitivity C-reactive protein (CRP), and matrix metalloproteinase-9 (MMP-9) (44). As described above, it has been demonstrated that statin therapies stabilize plaque by converting its components.

Ezetimibe reduces the absorption of cholesterol from the intestine by inhibiting the Niemann-Pick C1-like 1 (NPC1L1) protein and serves as another LDL-C-lowering agent (45). Recently, it was reported that ezetimibe helps to improve cardiovascular outcomes (46). The LDL-C level could be reduced by an additional 23% to 24% by the addition of ezetimibe to statins (46-48). With regard to its effect on plaque composition, it has been shown that ezetimibe, when added to fluvastatin, increased the fibrous cap thickness and reduced lipid plaque (49).

Despite these impressive cardioprotective effects of lowering the LDL-C level, the residual risk is still very important. Statins can reduce cardiovascular events by no more than 40% (50). In the SATURN (34) (Effect of Rosuvastatin versus Atorvastatin) and ASTEROID (28) (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) studies, coronary plaques progressed in approximately 30% of patients despite low LDL-C levels. This residual risk is related to the presence of small dense LDL, triglyceride, low levels of high-density lipoprotein cholesterol (HDL-C) and DM.

High-density lipoprotein (HDL)

Various epidemiological studies have revealed that HDL-C levels are inversely related to the risk of ASCVDs (51-54). In the Framingham Heart Study, a low level of HDL-C was shown to be a predictor of coronary heart disease, independent of LDL-C levels (55). The treating to new targets (TNT) study demonstrated that a low HDL-C level remains a good predictor of MACE even when an LDL-C level of under 70 mg/dL has been achieved with statins (56). Thus, a low level of HDL-C is recognized as a strong and independent risk factor for ASCVDs (57). This favorable effect of HDL-C is thought to be attributable to several atheroprotective effects of HDL (58). A classical interpretation is that HDL promotes the transport of excess cholesterol from macrophage cells in peripheral tissues to the liver (i.e., cholesterol efflux capacity). In addition, HDL has anti-oxidant, anti-inflammatory, anti-thrombotic or fibrinolytic activities, and improves endothelial function

by activating endothelial nitric oxide (NO) synthase. Based on these anti-atherosclerotic activities, HDL-C-targeted therapies have been advocated.

With regard to coronary atherosclerosis, it has been demonstrated in a pool analysis of 1,455 patients using IVUS that raising HDL-C levels by more than 7.5% was associated with plaque regression in patients who achieved LDL-C under 87.5 mg/dL with statins (59). Furthermore, another study of 261 consecutive ACS patients reported that the HDL-C level was positively associated with fibrous-cap thickness. They suggested that HDL-C has potential to be a beneficial therapeutic target for plaque stabilization (60).

However, these past studies failed to show an association between an increase in the HDL-C level and a reduction in the risk of ASCVDs (61,62). In the AIM-HIGH trial, there was no clinical benefit in patients with ASCVD with the addition of niacin to statin therapy, despite significant increases in HDL cholesterol levels (from 35 to 42 mg/dL) and decreases in triglyceride levels (from 164 to 122 mg/dL) (63). Addition of the cholesterol ester transfer protein (CETP) inhibitor dalcetrapib increased HDL cholesterol levels from baseline by 31% to 40% in patients with ACS, but did not have significant effect on major cardiovascular outcomes including the rates of myocardial infarction and death from coronary heart disease (64).

As a result, the quality of HDL, or HDL function, rather than its quantity, has lately been the focus of increasing attention. Khera *et al*. reported that the cholesterol efflux capacity of HDL was strongly and inversely associated with the likelihood of angiographic coronary disease, independent of the HDL cholesterol level (65). In addition, the cholesterol efflux capacity of HDL has been shown to be inversely associated with the incidence of cardiovascular events (66).

Apolipoprotein A-I (apoA-I), which contains 243 amino acids and is a major component protein of HDL, plays important roles in HDL function. Various basic studies have been performed using recombinant HDL [apoA-I Milano (67), CER-001 (68)], apoA-I mimetic peptides (69), reconstituted HDL [rHDL (70), CSL-111 (71)], delipidated HDL (72), and antagonist of microRNA-33 (Anti-miR33) (73). ApoA-I mimetic peptides are a major example; the 5F peptide inhibits the formation of aortic plaque in mice receiving a high-fat diet, which is the first in vivo demonstration that apoA-I mimetic peptides have atheroprotective properties (74). An ApoA-I mimetic peptide that contains 24 amino acids without phospholipids, Fukuoka University ApoA-I Mimetic Peptide (FAMP), enhanced HDL function and suppressed aortic plaque formation in apoE KO mice (75). In human studies, intravenous administration of ETC-216 (an apoA-I Milano/1-palmitoyl-2-oleoyl phosphatidylcholine complex) was associated with the significant regression of coronary atherosclerotic plaques as measured by IVUS (76). After the infusion of ETC-216, coronary plaque regression was accompanied by reverse remodeling of external elastic membrane (EEM) without changes in luminal dimensions (77). On the other hand, the ERASE (Effect of reconstituted HDL on Atherosclerosis-Safety and Efficacy) study, which used CSL-111 (reconstituted HDL consisting of apoA-I from human plasma combined with soybean phosphatidylcholine), resulted in no significant reductions in the percentage change in both plaque and atheroma volume, but significantly improved plaque characterization indexes on IVUS and coronary stenosis scores on quantitative coronary angiography (QCA) (78). Moreover, autologous delipidated HDL plasma treatment for ACS patients reduced the changes in total atheroma volume from baseline as analyzed by IVUS (delipidated group *vs*. control group, −12.2±36.8 *vs*. 2.8±21.3 mm^3). Plasma-selective delipidation converted the levels of preβ-like HDL and α-HDL from 5.6% to 79.1% and 92.8% to 20.9%, respectively. These changes in HDL subfraction may be a key point in support of the favorable effects of delipidated HDL. The level of preβ-HDL, which is the primary acceptor of cholesterol efflux by the ABCA1 transporter, is positively associated with efflux capacity in vitro. Among various HDL functions, efflux capacity and anti-inflammatory activities in particular may have potential to play crucial roles in stabilizing coronary plaques. The potential of these new approaches based on HDL-targeted therapies is substantial, and the results of human studies are eagerly awaited.

Diabetes mellitus (DM)

DM is associated with a higher morbidity of ASCVDs (79-81). Along with other clinical trials (26,82,83), the Copenhagen City Heart Study showed that the relative risk of the incidence of myocardial infarction in DM was 2- to 3-fold greater than that in non-DM, independent of the presence of other established risk factors (84). IVUS studies showed that DM accelerated the development of coronary atherosclerosis (85). Coronary specimens from patients with DM contained larger lipid-rich atheroma, infiltrated macrophages, and thrombosis than those from non-DM

patients (86).

Even in the absence of DM, higher blood glucose levels, higher hemoglobin A1c levels, and insulin resistance (IR) have been shown to be associated with an increased risk of ASCVDs (87-89). IR plays crucial roles in atherosclerosis (90), and it has been clarified that IR was positively associated with coronary severity (91), the coronary calcium score (92), and a remodeling index (93). Various past studies in basic research have supported the results of these clinical trials. They have also linked not only diabetes (94,95) but also glucose tolerance (96,97) to endothelial dysfunction, which is the initial step in the development of atherosclerotic plaque.

Metformin and thiazolidinediones (TZDs) are well-known to improve IR. The UK Prospective Diabetes Study (UKPDS) Group showed that metformin was superior to diet, sulfonylurea, and insulin with respect to survival benefit and cardiovascular protection (98). Although there is some evidence to support the use of metformin in basic science (99) and some retrospective analyses have indicated that metformin reduced cardiovascular-related morbidity and mortality in type 2 diabetes (100), there is no solid evidence to support the use of metformin for ASCVDs (101). Further randomized, double-blind clinical trials on metformin will be needed in the future.

TZDs are ligands for peroxisome proliferative-activated receptor-γ (PPARγ), which mainly resides in adipose tissue and ameliorates insulin sensitivity. This improvement in insulin sensitivity by TZDs leads to the reduction of blood glucose levels and hemoglobin A1c levels, suppresses inflammation, lowers blood pressure, and decreases urinary proteins (102,103). The PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study failed to prove that pioglitazone had a beneficial effect on the primary endpoint, i.e., the reduction of coronary and peripheral events. Nevertheless, the risk-reduction effect for the secondary endpoint, which was a composite of death, non-fatal myocardial infarction, and stroke, was significantly less than that with the placebo (104). In addition, the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) trial reported that pioglitazone showed a significantly slower progression of coronary atherosclerotic plaques compared with glimepiride (105).

Hyperglycemia induces endothelial dysfunction via various mechanisms. After glucose molecules enter the vascular wall, hyperglycemia increases the expression of adhesion molecules, and produces less NO. NO plays key roles in vasodilation and the regulation of platelet activation. Moreover, hyperglycemia induces protein kinase C (PKC) activation, increases the formation of advanced glycation end-products (AGEs) (106), and produces reactive oxygen species (ROS) (107). Raising the intracellular glucose level increases the expression of glycoprotein Ib (GpIb), which is a mediator of platelet aggression (108). Furthermore, it was reported that insulin activated plasminogen activator inhibitor type 1 (PAI-1) (109).

Postprandial hyperglycemia has been established as a better predictor of cardiovascular events than fasting hyperglycemia (110,111). Postprandial hyperglycemia induces oxidative stress, which leads to inflammation and endothelial dysfunction (112). α-glucosidase inhibitors (α-GIs), which delays carbohydrate digestion in the small intestine, have potential to prevent a glucose spike (the difference between the fasting glucose level and the peak level of postprandial hyperglycemia). In fact, both the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial (113) and a MeRIA (Meta-analysis of Risk Improvement under Acarbose) study (114) reported that α-GI acarbose could prevent future cardiovascular events.

Whereas the avoidance of hyperglycemia seems to be important for reducing cardiovascular events, recent clinical trials of intensive glucose-lowering in DM, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study and the VADT (Veterans Affairs Diabetes Trial) study, failed to demonstrate a reduction in cardiovascular events (115). An increased rate of hypoglycemia was considered to be one of the factors behind the excess mortality (116,117). Hypoglycemia induces increases in the amount of proinflammatory mediators and platelet activation (118), and this is mainly mediated by the sympathoadrenal system. In addition, hypoglycemia also induces endothelial dysfunction via the production of mitochondrial superoxide (119).

Based on these perspectives, the mean amplitude of glycemic excursion (MAGE) and glycemic variability (GV) have attracted considerable attention. GV has potential to more effectively trigger oxidative stress than chronic sustained hyperglycemia (120). It has also been advocated that GV may be associated with diabetic complications including cardiovascular events (121). It has been shown that GV derived from a continuous glucose monitoring system (CGMS) is an independent predictor of MACE in

AMI with type 2 diabetes (odds ratio 1.592; 95% CI, 1.034–2.451) (122). In addition, another group demonstrated that MAGE in a plaque-rupture group was significantly higher than that in a non-rupture group (123). Recently, it was clarified that glucose fluctuation may affect the formation of lipid-rich plaques and thinning of the fibrous cap in patients with optimal lipid treatment. The study population consisted of 85% patients with glucose metabolism disorder. In this study, MAGE was the only independent predictor of the presence of TCFA (124). Thus, it may be important to consider MAGE in the treatment of DM by using diabetic agents, such as α-GIs, TZDs, metformin, and incretins, which do not induce hypoglycemia except when administered in combination with sulfonylureas and insulin.

Hypertension

Blood pressure has been shown to be a strong predictor of cardiovascular deaths (125,126). In fact, it was demonstrated that an increase in systolic and diastolic blood pressure of 20/10 mmHg doubles the risk for cardiovascular disease (127). It is also well known that hypertension increases atherosclerotic plaques (128,129). The reduction of blood pressure through lifestyle modification and/or blood pressure-lowering agents dramatically reduced the risk of ASCVDs (130-132). Consequently various therapeutic agents for lowering blood pressure have been developed, i.e., angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), β-blockers, and calcium channel blockers (CCBs).

Activation of the renin-angiotensin system (RAS) plays important roles in cardiovascular events (133). In fact, the HOPE (Heart Outcomes Prevention Evaluation) study showed clinically that RAS inhibition not only lowers blood pressure but is also vasoprotective (134). In this study, the ACE-I ramipril significantly reduced the rates of death (relative risk 0.74; 95% CI, 0.64–0.87 compared with the placebo group), myocardial infarction (relative risk 0.80; 95% CI, 0.70–0.90), and stroke (relative risk 0.68; 95% CI, 0.56–0.84) in high-risk patients (≥55 years old who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor) without evidence of left ventricular systolic dysfunction or heart failure. Similarly, the EUROPA (European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) study showed that blood pressure-lowering by 5 mmHg with perindopril reduced the cardiovascular risk by 20% among patients with stable angina without apparent heart failure (135).

There is a connection between the activation of RAS and the formation of thrombus, e.g., angiotensin II (Ang II) activates PAI-1 in ECs (136). The pleiotropic effects of ACE-Is on platelet aggregation have been reported in a clinical study (137). The inhibition of RAS by ACE-Is and ARBs leads to a reduction in ROS, suppression of the activation of redox-sensitive pro-inflammatory transcription factors, and the maintenance of NO production in endothelial cells (ECs) (138). The reduction of free radicals by the inhibition of xanthine oxidase and the reduction of LDL oxidation by ACE-Is brings about plaque stabilization (139). In a rabbit plaque model, ACE-Is and ARBs increased collagen content, VSMCs, and the thickness of TCFA (140). Clinical studies have shown that coronary atherosclerotic plaque volume, as measured by IVUS, significantly decreased after ARB treatment (141-143). ARBs have potential to decrease inflammatory infiltration, increase collagen content and stabilize human carotid plaques (144). Another favorable effect of ARBs beyond their ability to lower blood pressure is the prevention of blood vessel aging by suppressing the senescence of ECs and VSMCs (145-147). In these ways, ACE-Is and ARBs, which block activation of the RAS, may confer a cardioprotective effect beyond their ability to lower blood pressure.

There is abundant evidence on the relation between CCBs and cerebrovascular diseases (148). The PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial) showed that a long-acting CCB significantly regressed carotid arteriosclerosis. Another important finding of this trial was that amlodipine reduced the rates of unstable angina and coronary revascularization (149). The CAPARES (Coronary Angioplasty Amlodipine Restenosis Study) also showed a reduction of coronary revascularization (150). The vasorelaxant effect of CCBs, i.e., the regulation of NO production, prevents the formation of abnormal vasoconstrictions, which can lead to plaque rupture. Several atheroprotective effects of amlodipine may also contribute to these results. It has the capacity to inhibit lipid oxidative modification (151,152), and subsequently inflammatory responses (153).

β-blockers have been used as therapeutic drugs for hypertension for more than 50 years (154). Their efficacies in congestive heart failure and angina have been well established. β-blockers are particularly effective for preventing recurrent ASCVD events in patients with ACS (130). Some β-blockers also have the ability to block

the oxidation of LDL, which leads to foam cell formation and the augmentation of atherosclerotic plaque (155). However, their association with plaque stability is not clear. Further research on the relationship between β-blockers and coronary atherosclerotic plaque stability will be required.

Smoking

Cigarette smoking increases the risk of AMI more than that of stable angina (156). Active and passive smoking are strong risk factors for AMI (157). It has been demonstrated that plaque in smokers contains higher levels of extracellular lipid (158). Eroded plaque was associated with smoking, especially in women, compared with ruptured plaque (159). The mechanisms by which smoking promotes atherosclerotic lesions or erosion are not completely elucidated.

Smoking is associated with endothelial dysfunction (160), which is restored by smoking cessation. Toxic gas-phase substances in tobacco damage vascular endothelium due to their proinflammatory effects. Smoking elevates the expression of soluble adhesion molecules, vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) in ECs. Exposure to cigarette smoke increased intraplaque inflammation and neovascularization, which leads to intraplaque hemorrhage and consequent necrotic core formation (160). Nicotine affects serum thromboxanes A2/B2 and catecholamines, which enhance platelet activation (12). Cigarette smoke extracts decreased prolyl-4-hydroxylase (P4H) expression, which is essential for the folding of newly synthesized collagen polypeptide chains into triple-helical molecules, in ECs and smooth muscle cells, which leads to decreased vascular collagen production (161). Basic research clarified that smoking-induced oxidative stress and inflammation have potential to increase MMP gene expression (162). In fact, smoking was shown to increase MMPs in patients with AMI (163).

With regard to lipids, it is well known that smoking increases the level of LDL-C (164). Nevertheless, a meta-analysis reported that there was no significant change in LDL-C after smoking cessation (165). It was reported that smoking cessation leads to improved HDL functionality (efflux capacity and anti-inflammatory property) (166).

These mechanisms may contribute to the plaque instability and thinning of the fibrous cap by smoking, and to stabilized plaque after smoking cessation. The cessation of smoking, such as with an anti-tobacco program, can lead to the reduction of the risk of tobacco-related ASCVDs events, especially in AMI.

Inflammation

The relationship between atherosclerosis and inflammation has been well established (167). The REVERSAL trial showed a 36.4% reduction in CRP in the atorvastatin group compared with a 5.2% reduction in the pravastatin group, which was an independent predictor of a reduction in plaque progression (32). The SATURN study demonstrated that, after 24 months of statin therapy, non-increasing levels of CRP were independently associated with greater percent atheroma volume regression, and the on-treatment CRP level was significantly associated with MACE (168). The JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showed that statin therapy is effective at preventing cardiovascular events in healthy persons without hyperlipidemia but with elevated levels of high-sensitivity CRP. This trial was stopped early after a median follow-up of 1.9 years since there was a 44% reduction in the primary endpoint of all vascular events, a 54% reduction in myocardial infarction, and a 48% reduction in stroke in the rosuvastatin group compared with the placebo (169).

The responses that serve to protect us against inflammation are called immunity, and these consist of natural and adaptive immunities. T cells play a particularly important role in adaptive immunity, and are considered to be highly involved in the process of atherosclerosis (170). It is well known that $CD4^+$ T helper (Th) cells can differentiate into some distinct subsets, i.e., Th type 1 (Th 1), Th type 2 (Th 2), Th type 17 (Th 17), and T regulatory cells (Tregs), which can be distinguished from one another by their cytokine profiles (171). Th 1 produces interferon (INF)-γ, interleukin (IL)-2, and IL-12. Th 2 produces IL-4, IL-5, IL-10, and IL-13. Th 17 produces IL-17 and IL-22. Tregs can suppress inflammatory responses by various mechanisms.

Each of these subsets plays different roles, and it has been reported that the Th cell-mediated immune response is related to the development of atherosclerotic plaque. Th 1/Tregs have proatherogenic/atheroprotective effects. Th 1 cells play roles in the activation of macrophages, neutrophils, and cytotoxic T lymphocytes. Th 1 cells are related to atherosclerosis, rheumatoid arthritis (172), type 1 DM (173,174), multiple sclerosis, and graft-versus-host disease (GVHD) (175). As for atherosclerosis, the presence of Th 1 in human atherosclerotic plaque and a

positive relationship between Th 1 activity and coronary artery disease have been reported (176). Oxidized LDL, LDL, and heat shock protein 60 (HSP60) activated Th 1 in atherosclerotic plaque as the relevant activating antigen (177-179). In an atherogenic state, Th 1 produces large amounts of INF-ɤ, resulting in the overexpression of MMPs, the reduction of collagen production, and thinning of the fibrous-cap (180,181). In contrast to Th 1, Tregs can suppress inflammatory responses by various mechanisms (182-186). Tregs serve to maintain immunological tolerance and suppress effector T cell responses (187). The atheroprotective effect of Tregs on atherosclerosis has been reported in both a mouse model and a human study (188,189).

The roles of Th 2 and Th 17 are not completely understood. Th 2 has a stimulatory effect on antibody production and promotes the neutralization of microbes and toxins. It has been considered to be predominant in abdominal aortic aneurysm (190) and allergic diseases (191,192). The effect of Th 2 on atherosclerosis is controversial, since, while IL-5 and IL-13 show atheroprotective effects (193,194), IL-4 may promote atherosclerosis (195,196). As for IL-17, a study on specimens of human atherosclerotic plaque revealed that IL-17 promoted plaque vulnerability (197). However, it has also been reported that a deficiency of IL-17 could result in vulnerable plaque by reducing collagen and VSMCs. Similar unclear results have been reported in other studies (198-202). Further studies are needed to elucidate the roles of IL-17 in atherosclerosis.

Accumulating evidence suggests that it might be possible that the balance of Th cells is important, i.e., a Th 1/Th 2 imbalance may result in atherosclerosis (203). For instance, it has been reported that Th 1 is predominant in ACS (204,205) and unstable angina pectoris (206-208). Similarly, a Th 17/Tregs imbalance has been associated with plaque destabilization and its progression (209,210).

As described above, statins are widely used for the reduction of LDL-C and plaque stabilization. They are also useful with respect to the relationship between inflammation and Th cells. Statins may mainly suppress Th1 activity in the acute phase of ACS. After the administration of rosuvastatin, there was a reduction in the pro-inflammatory cytokines that are related to Th 1 (INF-γ). On the other hand, there was no change in the anti-inflammatory cytokines that are related to Th 2 (IL-4 and IL-10) (211). It has been reported that statins promote the differentiation of Tregs (212), and restrain the differentiation of Th 17 (213). Kruppel-like factor 2 (KLF2), which regulates the expression of molecules essential for naive T cell recirculation and the maintenance of T cell quiescence, plays a key role in this mechanism (214).

HDL also has potential to suppress the immune response of Th 1 and Th 17 by modulating dendritic cell maturation and function (215). On the other hand, an inverse relationship has been reported between Tregs and the HDL-C level (216). Further studies are needed to elucidate the role of HDL in atherosclerosis.

Conclusions

A growing body of evidence indicates that plaque progression can be suppressed or even reversed by anti-atherosclerotic medications, especially statins. Currently, the plaque burden and composition, which can be elucidated by various imaging modalities, are the main targets for medical treatment. We are assessing the effects of anti-atherosclerotic medications not only in terms of the event rate but also using these imaging modalities. However, it is possible that these modalities evaluate only part of the plaque morphology, pathology, and cardiovascular outcome. The mechanisms of plaque vulnerability are not fully elucidated, and various projects are ongoing in not only basic research but also clinically. One of the important topics clinically is the arrival of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, which reduce LDL-C levels >50% in combination with statins, and which may have potential as an anti-atherosclerotic treatment, especially for high-risk patients. Ongoing and further studies should help to determine the most effective approach to stabilize atherosclerotic plaque and improve the cardiovascular outcome.

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Footnote

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