Treatment B) Drug Therapy

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan – 2012 Version


Committee for Epidemiology and Clinical Management of Atherosclerosis

1. Drug Therapy

“Evidence-based medical therapy from the results of large-scale clinical trials” has been emphasized, and drug therapy is widely used for both primary and secondary prevention. However, with respect to the prevention of atherosclerotic cardiovascular disease (CVD), the basis for treatment is lifestyle modification, such as changing dietary habits, increasing physical activity, maintaining an ideal body weight and quitting smoking. In particular, in primary prevention, the risk factors for atherosclerosis should be evaluated correctly and treatment should be selected depending on the patient’s risk. In other words, it is important to not only ascertain the presence or absence of coronary artery disease (CAD) and measure the LDL-cholesterol (LDL-C) level, but also identify other major risk factors, including complications of CVD other than CAD, such as non-cardiogenic cerebral infarction, peripheral arterial disease (PAD) and carotid atherosclerosis, and complications of diabetes mellitus (DM) or chronic kidney disease (CKD), and then to perform an absolute risk evaluation and provide lipid management based on the guidelines. On the other hand, in secondary prevention, providing strict lipid management is essential, and the need for drug therapy is significant. Additionally, in secondary prevention patients, risks should be stratified, and more strict lipid-lowering therapy should be considered in those at a higher risk of recurrence.

2. Indications for Drug Therapy

1) LDL-C-Lowering Drugs

The absolute risk of CAD in the Japanese population is relatively low compared to that observed in Western populations, while the relative risk of LDL-C and CAD in Japanese patients is similar to that observed in Western patients. In the MEGA study1), a large-scale clinical trial in Japan, the significance of LDL-C-lowering therapy using statins for primary prevention in patients with hypercholesterolemia was confirmed in a Japanese population. However, in primary prevention, drug therapy should not be selected without carefully considering the individual’s risk; such therapy should be considered only in patients with a high absolute risk. Low-risk patients without any additional risk factors, young individuals and premenopausal women at low absolute risk can be followed up with lifestyle modification only, even if the management target is not achieved. Following strict lifestyle modification, and only if the management target is not achieved, drug therapy should be considered according to the level of risk. However, if a patient persistently has an LDL-C level of ≥180 mg/dL, considering drug therapy given the possibility of familial hypercholesterolemia (FH) is appropriate (see committee report 9: Familial Hypercholesterolemia).

Meanwhile, if type 2 diabetes, CKD, non-cardiogenic cerebral infarction or PAD is observed, the disease itself puts the patient at high risk for cardiovascular events. In such cases, strict lipid management based on the treatment/management guidelines is therefore required, and strict LDL-C-lowering therapy involving drug therapy should be considered at an early stage.

Large-scale clinical trials in secondary prevention patients, including the 4S, CARE and LIPID trials, have reported that LDL-C-lowering therapy using statins is effective. Subsequently, the safety and effectiveness of statin treatment in reducing cardiovascular
events after acute coronary syndrome were reported\textsuperscript{2-5}). Providing early strict lipid management is important for the long-term inhibition of cardiovascular events\textsuperscript{4, 6, 7}). The development of statins with more potent LDL-C-lowering effects has improved the rates of achievement of LDL-C management targets in Western countries and Japan, while the rates of achievement of management targets in secondary prevention patients remain insufficient. Therefore, in order to achieve the target of LDL-C < 100 mg/dL in the setting of secondary prevention, the use of lifestyle modification along with drug therapy is required. In secondary prevention, among patients at higher risk, such as those with acute coronary syndrome, current smoking habits, CAD complicated by metabolic syndrome, type 2 diabetes, non-cardiogenic cerebral infarction, PAD or CKD, achieving the LDL-C target (< 100 mg/dL) is essential and providing early, strict LDL-C management using drug therapy is important.

2) TG-Lowering Drugs and HDL-C-Increasing Drugs

Large-scale clinical studies in patients with high triglyceride (TG), low HDL-C and normal LDL-C levels have not shown as much positive evidence as that for LDL-C-lowering therapy\textsuperscript{8-12}). However, the subanalysis of the ACCORD Lipid Trial\textsuperscript{13)} revealed that combination therapy with fibrates and statins is effective in patients with high TG and low HDL-C levels; thus, further investigation is warranted. If the TG level is high, using the non HDL-C level as the lipid management target is recommended; however, there is little evidence with respect to using non HDL-C as a target, and thus continued discussion is required. In case of primary prevention, encouraging lifestyle modification with the primary goal of lipid management using the LDL-C level as a target is important. In patients with a remarkably increased TG level of \( \geq 1,000 \) mg/dL, dietary interventions, such as lipid restriction and alcohol abstinence, along with treatment with fibrates should be considered, because they have a high risk for acute pancreatitis.

Additionally, in patients with a history of CAD, similar to that observed in primary prevention, there is insufficient evidence for the use of drug therapy for dyslipidemia without hyper-LDL cholesterolemia. However, in secondary prevention patients at higher risk for recurrence of cardiovascular events, in addition to providing management of the LDL-C level at \(< 100 \) mg/dL, the use of combination drug therapy with drugs other than statins, such as fibrates and nicotinic acid derivatives, can be considered according to the type of dyslipidemia.

There are many reports regarding treatment evidence, suggesting the appropriateness of drug therapy. These reports are summarized in the reference tables at the end of the guidelines.

3. Characteristics and Criteria for Selecting Various Drugs

The classification of drugs used to treat dyslipidemia according to efficacy is shown in Table 1. The efficacy of these drugs was confirmed using a double-blind method in Japan. The characteristics and efficacy of various drugs should be understood, and selecting safe and effective drugs should be undertaken taking into consideration the presence of comorbidities and the possibility for drug interactions. The characteristics of various drugs used to treat dyslipidemia are described below.

1) HMG-CoA Reductase Inhibitors (Statins): Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Pitavastatin and Rosuvastatin

Statins are indicated for the treatment of dyslipidemia with a high LDL-C level.

Since the effect was shown in FH patients\textsuperscript{14)}, statins are the most effective in decreasing the LDL-C level among the lipid-lowering drugs. Statins competitively inhibit HMG-CoA reductases, the rate-limiting enzymes of cholesterol synthesis, inhibit cholesterol synthesis\textsuperscript{15)}, promote the synthesis of LDL receptors and decrease serum LDL-C\textsuperscript{16)}. The degree of LDL-C-lowering ranges from 20% to 50%. Furthermore, the inhibition of VLDL synthesis and secretion in the liver due to decreased cholesterol synthesis also results in a decreased TG level\textsuperscript{17); however, the degree of lowering is only approximately 10% to 20%. Reported adverse drug reactions include hepatic disorders and myopathic symptoms, such as increased creatinine kinase (CK) and muscular weakness. Rhabdomyolysis characterized by increased myoglobin in the blood and urine has also been reported, although this complication is very rare. This risk is increased by combining statins with fibrates, nicotinic acid derivatives, cyclosporine or erythromycin.

Previous reports have demonstrated that patients who use statins incidentally during early pregnancy can experience suspected teratogenicity\textsuperscript{18}; therefore, at present, statins should not be used in women who wish to become pregnant and patients in pregnancy.

2) Anion Exchange Resins (Resins): Colestipol and Cholestyramine

Resins are indicated for the treatment of dyslipidemia with a high LDL-C level (type IIa). Although the first-line drugs for hyper-LDL cholesterolemia are
and thyroid gland preparations; therefore, when these drugs are concomitantly used, instructions to take the drugs at a suitable interval must be provided to ensure drug efficacy.

3) Probucol

Probucol is indicated for the treatment of dyslipidemia with a high LDL-C level (type IIa). This drug is characterized by its effects of regression on xanthomas. However, this drug decreases both the LDL-C and HDL-C levels. The degree to which probucol lowers LDL-C is 15% to 25%. The mechanism underlying this phenomenon is thought to involve enhanced LDL catabolism, particularly via the promotion of cholesterol excretion in bile. In contrast, the mechanism underlying the decreased HDL-C level is thought to involve the inhibition of ABCA1, a membrane protein essential for HDL production. Other possible mechanisms include the enhanced activity of cholesterol ester transfer proteins (CETPs) and enhanced activity of SR-BI, an HDL receptor. From the viewpoint of cell biological factors and immunohistological factors and other factors, LDL-C oxidation is clearly an important aspect of the pathogenic mechanisms of atherosclerosis. Probucol is taken up by lipoproteins, after which it exerts potent antioxidant effects due to its structure in which two fat-soluble butylated hydroxytoluene (BHT) antioxidants are bound. An early clinical study demonstrated that cholestyramine treatment in combination with additional probucol exerts no inhibitory

<table>
<thead>
<tr>
<th>Classification</th>
<th>LDL-C</th>
<th>TG</th>
<th>HDL-C</th>
<th>Non HDL-C</th>
<th>Major generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>↓↓↓</td>
<td>↓</td>
<td>↑</td>
<td>↓↓</td>
<td>pravastatin,* simvastatin,* fluvastatin,* atorvastatin,* pitavastatin* and rosuvastatin</td>
</tr>
<tr>
<td>Anion exchange resins</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>↓↓</td>
<td>colestimide and cholestyramine</td>
</tr>
<tr>
<td>Small intestine cholesterol transporter inhibitor</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>↓↓</td>
<td>ezetimibe</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓</td>
<td>↓↓↓</td>
<td>↑↑</td>
<td>↓</td>
<td>bezafibrate,* fenofibrate, clinofibrate* and clofibrate*</td>
</tr>
<tr>
<td>Nicotinic acid derivatives</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
<td>niceritrol, nicomol* and tocopheryl nicotinate*</td>
</tr>
<tr>
<td>Probucol</td>
<td>↓</td>
<td>–</td>
<td>↓↓</td>
<td>↓</td>
<td>probucol*</td>
</tr>
<tr>
<td>ω3PUFA</td>
<td>–</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>ethyl icosapentate* and omega-3-acid ethyl esters</td>
</tr>
</tbody>
</table>

*A generic drug is available. PUFA: polyunsaturated fatty acid
↓↓↓: ≤ −25%; ↓↓: −20 to −25%; ↓: −10 to −20%; ↑: 10 to 20%; ↑↑: 20 to 30%
effects on the progression of atherosclerosis in the femoral artery on angiography. However, subsequent clinical studies and observational studies demonstrated inhibitory effects on restenosis and improvements in long-term survival following percutaneous transluminal coronary angioplasty (PTCA), inhibitory effects on the progression of the carotid intima-media thickness (IMT), inhibitory effects on cardiovascular events and secondary prevention effects in patients with heterozygous FH. In any case, because no large-scale clinical studies have been conducted, the use of probucol is limited to combination therapy with statins and monotherapy in patients who cannot tolerate statins. Adverse drug reactions include gastrointestinal symptoms, hepatic disorders, rashes, QT prolongation and torsade de pointes on electrocardiograms.

4) Nicotinic Acid Derivatives: Niceritrol, Nicomol and Tocopheryl Nicotinate

Nicotinic acid derivatives are indicated for the treatment of hyper-LDL cholesterolemia, hypertriglycerideremia and dyslipidemia accompanied by increased remnant lipoproteins.

The mechanism of action of these drugs involves the inhibition of hormone-sensitive lipases, thereby inhibiting lipolysis in peripheral fatty tissue and decreasing the influx of free fatty acids into the liver, resulting in the inhibition of lipoprotein synthesis in the liver. In addition, these drugs exert HDL-C-increasing effects by inhibiting apolipoprotein A-I catabolism. The rate of decrease in TG following nicotinic acid monotherapy is 26%. Nicotinic acid derivatives also have Lp(a)-lowering effects. Major adverse drug reactions include itching and hot flashes due to peripheral vasodilation. Because insulin resistance may be exacerbated, these drugs should be carefully administered in patients with DM.

5) Fibrates: Bezafibrate and Fenofibrate

Fibrates are most effective for hypertriglycerideremia. In particular, fibrates are markedly effective for type III hyperlipidemia because they enhance the catabolism of remnant lipoproteins. These drugs are also highly effective in increasing HDL-C.

The major mechanism of action is the activation of PPARα, a nuclear receptor, by fibrates acting as a ligand for PPARα, which results in the following: (i) enhanced beta-oxidation of fatty acids and decreased TG production in the liver; (ii) increased LPL production; (iii) decreased Apo C-III production and enhanced LPL activity, leading to the promotion of TG degradation and catabolism from VLDL to LDL; and (iv) increased production of Apo A-I and A-II. As a result, the TG level decreases and the HDL-C level increases. Bezafibrate has a TG-lowering effect of 30% to 40%, a TC-lowering effect of approximately 10% and an HDL-C-increasing effect of 35% to 45%. Fenofibrate is characterized by a long half-life, exerts an effect on lipids and has a uric acid-lowering effect. Regarding major adverse drug reactions, rhabdomyolysis is likely to occur in patients with renal dysfunction; the incidence of this complication increases in combination with statins.

6) EPA: Ethyl Icosapentate

EPA is indicated for the treatment of dyslipidemia accompanied by increased TG, especially for type IIb and IV hyperlipidemia. EPA inhibits VLDL synthesis in the liver, thereby decreasing the TG level, and has a slight HDL-C-increasing effect. The results of epidemiological studies and secondary prevention studies have demonstrated that the intake of fish oil and n-3 polyunsaturated fatty acids helps to prevent cardiovascular events. The JELIS study conducted in Japan found that patients who received statins in combination with additional EPA exhibited a significant reduction in the incidence of major cardiovascular events compared to patients who received statin monotherapy, indicating the efficacy of EPA. In addition to its effects on lipids, EPA is expected to have antiplatelet and anti-inflammatory effects in preventing atherosclerosis. Regarding major adverse drug reactions, gastrointestinal symptoms, such as diarrhea and bleeding, should be noted.

7) Small Intestine Cholesterol Transporter Inhibitor: Ezetimibe

This drug inhibits Niemann-Pick C1-Like 1 (NPC1L1), a small intestine cholesterol transporter that exists in the small intestinal mucosa and inhibits the absorption of cholesterol in the small intestine derived from diet and bile, thereby exerting a serum cholesterol-lowering effect. Unlike resins, this drug is absorbed in the body and enters the intestinal circulation, although approximately 78% of the drug is excreted in feces. Because this drug selectively inhibits cholesterol absorption, the absorption of fat-soluble vitamins, such as vitamins A and D, is not affected. The usual dose (10 mg/day) decreases the LDL-C level by approximately 18%, and, similar to resins, this drug enhances cholesterol synthesis in the liver. Therefore, the use of combination therapy with statins is ideal and also provides a synergistic effect; combination therapy with 10 mg of ezetimibe and a statin at a usual dose decreases the LDL-C level by approximately
35\% \text{ to } 50\%^{40-42}, \text{ which is equivalent to the effects achieved using a maximum dose of statin monotherapy. Furthermore, the HDL-C level is increased by 8\% \text{ to } 9\%, \text{ while the TG level is decreased by 20\% \text{ to } 30\%. Major adverse drug reactions include gastrointestinal symptoms; however, no significant differences are observed compared to a placebo. Similar to that observed with statins, myopathic symptoms, such as increased CK and muscular weakness, although rare, have been reported, and there are no reports indicating that the use of combination therapy with statins increases the incidence of adverse drug reactions.}

4. Combination Therapy

If the therapeutic target values for dyslipidemia are not achieved with treatment with a single agent, increasing the dose or administering combination therapy with other lipid-lowering drugs can be considered. In particular, in secondary prevention, when the target LDL-C value is less than 100 mg/dL, achieving the therapeutic goal with a single agent is sometimes difficult. In such cases, the use of combination therapy with several classes of agents should be considered. Upon the initiation of combination therapy, the characteristics of each drug described above should be fully considered in order to achieve maximal benefits and minimal adverse effects. Several studies performed in Western countries have shown that combination therapy is effective in inhibiting the progression or inducing the regression of atherosclerotic lesions. In these studies, combination therapy with statins and resins\(^{49}\) decreased the total cholesterol (TC) and LDL-C levels by 34\% and 46\%, respectively, while combination therapy with high dose of resins and nicotinic acid derivatives\(^{40, 44}\) decreased the LDL-C and TG levels up to 43\% and 22\%, respectively. Likewise, in Japan, combination therapy with pravastatin and colestipol\(^{41, 43}\) has been reported to decrease the TC and LDL-C levels by 26\% and 37\%, respectively, and increase the HDL-C level by 21\%, thus indicating the efficacy of combination therapy.

Combination therapies that have been proven to be effective in improving serum lipid profiles in Japanese populations include the following: (1) statins and resins\(^{45, 49, 46}\); (2) statins and fibrates\(^{47, 48}\); (3) statins and probucol\(^{49}\); (4) statins and nicotinic acid derivatives\(^{50}\); (5) probucol and nicotinic acid derivatives\(^{51}\); (6) statins, probucol and resins\(^{52, 53}\); and (7) statins and ezetimibe. The administration of statins in combination with ezetimibe or resins is theoretically the most effective means of decreasing the LDL-C level. Furthermore, the combination of statins and ezetimibe exerts TG-lowering and HDL-C-increasing effects. Combination therapy with statins and nicotinic acid derivatives results in decreased cholesterol and increased HDL-C levels. Among the above-mentioned combination therapies, the combination of statins and fibrates should be administered with caution because this combination has a high risk of inducing rhabdomyolysis. According to the postmarketing survey conducted under the instructions of the Ministry of Health, Labour and Welfare, most patients who develop rhabdomyolysis following the coadministration of statins and fibrates have renal disorders; thus, if laboratory tests reveal an abnormal renal function, the use of combination therapy with statins and fibrates should be avoided.

5. Follow-Up of Drug Therapy

Following the initiation of pharmacological intervention, the efficacy and side effects of the agent should be monitored. In general, monitoring the patient every month for the first three months and at least every three months thereafter is recommended. In order to detect side effects using blood tests, performing liver function tests [AST (GOT), ALT (GPT), LD (LDH), ALP, yGTP and total bilirubin], renal function tests (urinalysis, serum creatinine and BUN) and assessments of CK and blood cell counts is recommended.

6. Combination Therapy with Lipid-Lowering Drugs and Other Agents to Prevent Atherosclerosis

1) Precautions for Drug Combination

Fat-soluble drugs are excreted after being catabolized to water-soluble compounds by cytochrome P450 (CYP) in the liver. Among statins, drugs other than pravastatin and rosuvastatin are fat-soluble and metabolized by CYP. Because hypertension and dyslipidemia are common diseases, many patients suffer from both conditions; thus, the frequency of prescribing both antihypertensive and lipid-lowering agents is estimated to be high. Most calcium channel blockers (CCBs) and some angiotensin II receptor blockers (ARBs) are catabolized by CYP (Table 2); therefore, the coadministration of agents metabolized by the same CYP may increase the blood concentration of each agent, resulting in an increased incidence of adverse reactions. Thus far, no reports have documented an increased incidence of adverse events following the administration of combination therapy with statins and either CCBs or ARBs; however, attention must always be paid to possible drug interactions when these medications are coadministered.

Bile acid-binding resins adsorb drugs with negative charges. As a consequence, resins may cause
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Table 2. Statins and Cardiovascular Drugs Metabolized by CYP

<table>
<thead>
<tr>
<th>CYP</th>
<th>Statin</th>
<th>Cardiovascular drug</th>
</tr>
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<tbody>
<tr>
<td>CYP2C9</td>
<td>Fluvastatin</td>
<td>ARBs (losartan, valsartan, and candesartan) and warfarin</td>
</tr>
<tr>
<td></td>
<td>(Pitavastatin)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Rosuvastatin)*</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Simvastatin</td>
<td>Ca-antagonists (diltiazem, verapamil, nifedipine, amlodipine, clnidipine, azelnidipine, and benidipine) and warfarin</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin</td>
<td></td>
</tr>
</tbody>
</table>

*Pitavastatin and rosuvastatin are also minimally metabolized by CYP2C9.

delayed and/or decreased absorption of beta-blockers and thiazide diuretics. Furthermore, because resins theoretically inhibit the absorption of hydrophobic agents, they may inhibit the absorption of fat-soluble drugs, such as statins, CCBs and ARBs. Therefore, in patients who can adhere to a somewhat sophisticated medication schedule, taking fat-soluble drugs one to four hours before or ≥4 hours after taking a resin is recommended.

Warfarin is one of the most commonly prescribed agents for CVD; however, it interacts with many drugs. Therefore, caution should be taken when prescribing warfarin with other drugs. When warfarin is administered together with simvastatin, fluvastatin, rosvastatin or fibrates, its effects are augmented. In contrast, the effects of warfarin are reduced when administered with resins. Physicians must also keep in mind that the co-administration of EPA together with warfarin may increase the risk of hemorrhagic events, as EPA inhibits platelet aggregation.

2) Evidence for CVD Treatment Using Combination Therapy Consisting of Lipid-Lowering Agents and Antihypertensive Drugs

The ASCOT-LLA study is a large-scale clinical trial with a 2 × 2 design; the patients were assigned to receive either amlodipine or atenolol to treat hypertension, and each group was allocated to receive either atorvastatin or a placebo for lipid management. This study found that there were no differences in the efficacy of amlodipine and atenolol, while the incidence of CAD events was significantly decreased in the amlodipine-atorvastatin group compared to that observed in the atenolol-atorvastatin group.

Beta-blockers have been shown to be effective in inhibiting atherosclerosis. At present, no large-scale clinical trials have elucidated the effects on the rate of cardiovascular events following the coadministration of beta-blockers and lipid-lowering drugs. Nevertheless, the add-on administration of beta-blockers to statins has been demonstrated to exert inhibitory effects on the progression of IMT and and cause a regression of atherosclerotic plaques, as assessed on intravascular ultrasonography (IVUS).

Regarding renin-angiotensin system (RAS) inhibitors, studies evaluating coronary stenosis or stent restenosis on angiography have reported that combination therapy using RAS inhibitors together with statins results in favorable outcomes compared to that observed with monotherapy with either drug.

7. Adherence

Dyslipidemia is the largest risk factor for CVD. However, most patients, except for those undergoing secondary prevention therapy, do not experience symptoms. Therefore, a high proportion of patients do not recognize dyslipidemia as a disease. In addition, accepting the need to treat dyslipidemia unless provided an appropriate explanation by a medical professional is difficult. The rate of recognition of dyslipidemia has been reported to be lower than that of hypertension.

The basic therapy for preventing CVD is lifestyle modification, including diet therapy, exercise therapy and smoking cessation. In order for patients to appropriately achieve these lifestyle modifications, physicians and medical professionals must first establish a good relationship with the patient and their family members and fully explain the relationships between CVD, dyslipidemia and lifestyle factors. Furthermore, physicians and medical staff must confirm that the patient understands the explanation. Several techniques have been proposed to improve patient adherence, including the following: devising a feasible lifestyle modification program together with the patient; helping the patient to resolve problems encountered in daily life; advising and encouraging the patient; or instructing the patient to take gender into account. Furthermore, the benefits of lipid-lowering agents, if administered, are expected to be at their highest when the patient adequately achieves the lifestyle modifications.
In order to improve medication adherence, explaining the need to take medications is important\(^6\). In general, improvements in medication adherence lead to improvements in the benefits of the medication\(^5\). The use of a simpler dosing regimen involving the minimum number of tablets and the least complicated administration plan (once daily is best\(^6\)) results in improved adherence\(^6\). However, even the administration of once-daily drugs, such as statins, is associated with the following: the longer the treatment period, the lower the adherence over time\(^7\); patients without complications tend to exhibit decreased adherence\(^8\); and patients with good adherence one to two years after the initiation of drug therapy continue to exhibit good adherence to medication\(^9\). Therefore, explaining the need for drug treatment periodically and continuously is important. In addition, confirming the efficacy of the drug using blood tests following the initiation of treatment is necessary. Monitoring the data periodically (approximately every three months) to determine whether the therapeutic target has been reached and explaining the results to the patient is crucial for improving adherence\(^10\). With regard to drugs with relatively good adherence, such as statins, measuring the cholesterol levels is helpful for determining whether medication adherence is suitable\(^11\). However, it is important not to be content with simply measuring the LDL-C level, but rather to also assess each patient’s level of understanding regarding his/her current medical condition and the need for medication in the routine clinical setting\(^12\).

Among the various risk factors for atherosclerosis, dyslipidemia and hypertension are conditions that can be effectively managed with pharmacological intervention. Recently, a combination drug that includes a statin and CCB has become available in Japan. In Japan, 40% to 50% of patients with hypertension suffer from dyslipidemia. Of these patients, approximately 60% have been reported to receive treatment for dyslipidemia; however, ≥60% of patients receiving treatment have been reported to not achieve the therapeutic target values described in the guidelines issued in 2002. In particular, ≥80% of patients with a history of CAD have been reported to have not achieved the target\(^13\). Studies conducted in Western countries have shown that adherence to medications can be improved by changing to the aforementioned combination drug from the use of statins and CCBs separately\(^14\) and that adherence is notably better in patients who have previously taken either drug\(^15\).

Footnotes

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