Best Treatment Strategies With Statins to Maximize the Cardiometabolic Benefits

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Statins are important for preventing adverse cardiovascular events in patients with both high and low risk of vascular disease, by reducing the levels of low-density lipoprotein cholesterol (LDL-C). However, statins dose-dependently increase adverse effects and increase the risk of type 2 diabetes. Previously, it was hypothesized this was caused by off-target effects, but recent studies demonstrate it is caused by on-target effects. Nonetheless, the American guidelines recommend the use of high-intensity statin therapy, and extend its use to most people at risk of vascular diseases, particularly older people. In contrast, European, Korean, and Japanese committees have expressed concerns about the potential adverse effects of using high-intensity statins for lifelong periods in a large fraction of the population. Patients who have achieved LDL-C levels below currently recommended targets may still experience cardiovascular events, resulting from residual risk. Ezetimibe, PCSK9 inhibitors, inclisiran, and ANGPTL3 antisense oligonucleotides are promising alternative non-statin drugs. Of interest, cross-talk between hypercholesterolemia and the renin-angiotensin-system exists at multiple levels of insulin resistance and endothelial dysfunction. There are still unanswered questions on how to maximize the cardiometabolic benefits of statins in patients. We will discuss the results of randomized clinical trials, meta-analysis, and recent clinicopharmacogenetic studies, and propose practical guidelines to maximize the cardiometabolic benefits while reducing adverse effects and overcoming residual risk.

Key Words: Cardiovascular disease; Non-statins; Residual risk; Statins; Type 2 diabetes mellitus

Hypercholesterolemia is the most important and modifiable risk factor for cardiovascular (CV) disease (CVD). Many investigators have demonstrated the beneficial effects of statins on the risk of coronary artery disease (CAD) events by lowering low-density lipoprotein cholesterol (LDL-C) in patients with and without CVD.\(^1\)\(^-\)\(^5\) However, statins are associated with deteriorating glucose homeostasis\(^6\)\(^-\)\(^7\) and an increased risk of type 2 diabetes mellitus (T2DM),\(^8\)\(^-\)\(^9\) both of which are dose-dependent. There are still many unanswered questions on how to use statin therapy to optimize the simultaneous CV and metabolic benefits while minimizing the adverse effects and overcoming residual risk.

American guidelines target a reduction in overall CV risks by recommending the use of high-intensity statin therapy, but do not explicitly consider adverse metabolic actions of high-dose statins.\(^10\) European, Korean, and Japanese committees have expressed concerns about the potential adverse effects of high-intensity statin therapy for lifelong extended periods in a large fraction of the population.\(^11\)\(^-\)\(^14\) For example, the Japanese committee mentions that adverse effects are not so serious in Japan because the maximum allowable dose of statin is lower compared with other countries.\(^14\)

The unwanted metabolic effects of statins should be considered when formulating optimal therapeutic strategies to reduce overall morbidity and mortality, not just CV ones.\(^15\)\(^-\)\(^18\) Recent clinicopharmacogenetic studies demonstrated that the effect of statins on insulin resistance (IR) is an on-target effect,\(^19\)\(^,\)\(^20\) so more potent LDL-lowering efficacy increases the risk of T2DM because of both impaired insulin secretion and IR despite the reduction in CV morbidity and mortality. This would be more of a consideration in Asian people, because LDL-C levels are lower in Asians than in Caucasians.\(^21\) Also, the phenotype for T2DM in Asians is somewhat different than that in...
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Factors (15.5 vs. 7.7 events per 1,000 patient-years). Nearly twice as high as in those without additional risk in patients with at least 1 additional CV risk factor was found. A post-hoc analysis found that the incidence of CV events (e.g., 10-year risk >7.5% vs. >10%). In the JUPITER study, the risk threshold used to select patients for statin treatment was lower for patients with a 10-year risk of 25–40% or universally (10-year risk >40%) with an optimal LDL-C in the range of 70 mg/dL. The US Preventive Services Task Force recommends initiating use of low- to moderate-dose statins in adults aged 40–75 years without a history of CVD who have ≥1 CVD risk factors. The benefit was demonstrated with LDL-C <70 mg/dL. This hypothesis is diffr from prior ATP III guidelines recommending titration of the statin dosage to achieve target LDL-C levels, with the intensity of therapy determined by CV risk factors. Although there is a consensus on statin therapy according to the CV risk, the recommended dose varies among the countries. In the UK, the Joint British Societies recommend statin therapy in persons with a 10-year risk ≥10%. The International Atherosclerosis Society recommends no cholesterol-lowering medication for persons at low risk (10-year risk <15%); for persons at higher risk, medication use is optional (10-year risk of 15–24%) or generally (10-year risk of 25–40%) or universally (10-year risk >40%) with an optimal LDL-C in the range of 70 mg/dL. The US Preventive Services Task Force recommends initiating use of low- to moderate-dose statins in adults aged 40–75 years without a history of CVD who have ≥1 CVD risk factors and a calculated 10-year CVD event risk of ≥10% and concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use in adults aged ≥76 years (Table 1). A cohort study of 31,619 patients with ischemic heart disease who were adherent to statin treatment found a lower risk of major adverse cardiovascular events associated with achieved LDL-C levels <100 mg/dL, but no additional benefit was demonstrated with LDL-C <70 mg/dL. This does not support a blanket principle that lower LDL-C is better for all patients in secondary prevention.

Benefits of Statins are Dependent on the Individualized CV Risk

Statins revolutionized the treatment of hypercholesterolemia, and LDL-C-lowering therapy with statins can significantly reduce the incidence of CAD and mortality rates in patients with heart failure. The benefits of statins do not appear to be restricted to patients with elevated lipid levels, as similar effects are observed in subgroups stratified according to baseline total cholesterol or LDL-C levels. Given similar relative risk estimates, the absolute benefits of statin therapy will be greater in patients at high baseline risk. This has implications for determining the CV risk threshold used to select patients for statin treatment (e.g., 10-year risk >7.5% vs. >10%). In the JUPITER study, a post-hoc analysis found that the incidence of CV events in patients with at least 1 additional CV risk factor was nearly twice as high as in those without additional risk factors (15.5 vs. 7.7 events per 1,000 patient-years). However, there is no study that directly compares treatment with statins titrated to attain target cholesterol levels. In addition, little direct evidence is available to determine the effects of statin therapy intensity on clinical outcomes. An analysis of the association between degree of lipid reduction achieved and clinical outcomes may provide indirect evidence about the effects of statin intensity in patient groups. Recent guidelines from the ACC/AHA differ from prior ATP III guidelines recommending titration of the statin dosage to achieve target LDL-C levels, with the intensity of therapy determined by CV risk factors. Although there is a consensus on statin therapy according to the CV risk, the recommended dose varies among the countries. In the UK, the Joint British Societies recommend statin therapy in persons with a 10-year risk ≥10%. The International Atherosclerosis Society recommends no cholesterol-lowering medication for persons at low risk (10-year risk <15%); for persons at higher risk, medication use is optional (10-year risk of 15–24%) or generally (10-year risk of 25–40%) or universally (10-year risk >40%) with an optimal LDL-C in the range of 70 mg/dL. The US Preventive Services Task Force recommends initiating use of low- to moderate-dose statins in adults aged 40–75 years without a history of CVD who have ≥1 CVD risk factors and a calculated 10-year CVD event risk of ≥10% and concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use in adults aged ≥76 years (Table 1). A cohort study of 31,619 patients with ischemic heart disease who were adherent to statin treatment found a lower risk of major adverse cardiovascular events associated with achieved LDL-C levels <100 mg/dL, but no additional benefit was demonstrated with LDL-C <70 mg/dL. This does not support a blanket principle that lower LDL-C is better for all patients in secondary prevention.

On-Target or Off-Target Effect of Statins on Risk of T2DM

Most believe statins reduce the CV risk by lowering LDL-C levels; however, some hold the view that statins reduce the risk through multiple actions known as pleiotropic effects. The relative contribution of statin pleiotropy to clinical outcomes, however, remains a matter of debate and is hard to quantify despite the many RCTs denying pleiotropic effects because the degree of isoprenoid inhibition by statins correlates to some extent with the amount of LDL-C reduction. Indeed, this hypothesis is difficult to prove despite the clinical importance. Recently, this issue has been disputed. Namely, the primary mechanism of statins’ effect is to reduce LDL-C and atherogenic

Table 1. Target Levels of LDL-C in Current Guidelines

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<tr>
<td>ACS, IHD, CVA, PAD</td>
<td>LDL-C &lt;50%↓</td>
<td>LDL-C &lt;70 mg/dL (1.8 mmol/L)</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
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<tr>
<td>T2DM with Cx</td>
<td>LDL-C &lt;50%↓</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
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<tr>
<td>CAD equivalent</td>
<td>LDL-C &lt;50%↓</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
</tr>
<tr>
<td>DM without Cx, CAD, abdominal aneurysm</td>
<td>LDL-C &lt;50%↓</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;100 mg/dL (2.5 mmol/L)</td>
<td>LDL-C &lt;100 mg/dL</td>
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Primary prevention

| Intermediate risk (≥2 risk factors) | LDL-C <50%↓ | LDL-C <70 mg/dL | LDL-C <130 mg/dL (3.3 mmol/L) | LDL-C <120 mg/dL (4.2 mmol/L) |
| Low risk (≤1 risk factor)          | LDL-C <50%↓ | LDL-C <70 mg/dL | *LDL-C <160 mg/dL (4.2 mmol/L) |

ACS, acute coronary syndrome; CAD, coronary artery disease; CVA, cerebrovascular accident; Cx, complication; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus.
lipoproteins. RCTs of statins show that atherosclerotic CV disease (ASCVD) reduction is proportional to LDL-C lowering. A recent meta-regression analysis also showed that lower achieved LDL-C levels were associated with lower rates of major coronary events. Statins are similar to other LDL-lowering agents and are not unique except for their LDL-lowering potency.

On the other hand, statins dose-dependently worsen insulin sensitivity by reducing plasma levels of adiponectin and increase the risk of T2DM in humans. This was considered to be an off-target effect of statins, but the results of recent genetic studies denied the off-target effect of statins on the risk of T2DM. They clearly demonstrated that exposure to LDL-C-lowering genetic variants was associated with a higher risk of T2DM despite a significant reduction in coronary artery disease risk. Furthermore, the effects of these variants were independent and additive. These studies re-ignite the debate of whether the reduction in CV risk is mediated by on- or off-target effects and provide insights into potential adverse effects of high-intensity dosing of statins.

Blood glucose homeostasis. Indeed, the ideal therapy would simultaneously lower LDL-C to target levels while reducing the risk of T2DM and progression of existing T2DM instead of increasing it. One mechanism by which statins may increase the risk of T2DM is through a modest increase in body weight, increased IR and decreased β cell function. Further, the physiological mechanisms evaluated in this study support our previous studies suggesting that the major cause of statin-induced T2DM is reduced insulin secretion and increased IR. Evidence from genetic analysis and RCTs suggests that the increased risk of T2DM noted with statins is at least partially explained by 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibition. In a stratified analysis of the JUPITER data, participants with ≥1 T2DM risk factor were at higher risk of incident T2DM than those without T2DM risk factors. By contrast, in individuals with no major T2DM risk factors, rosuvastatin treatment did not cause T2DM and reduced CV events by 52%, 13% more than in the former group. This may just be because it is easier to detect adverse metabolic actions in patients with more risk factors. Recent genetic studies clearly demonstrated this. PCSK9 inhibitors and statins use distinct mechanisms to lower LDL-C, the common downstream effect that is likely related to both protection against CVD and promotion of T2DM. In subjects with preexisting glucose intolerance, variants in both genes were also associated with independent and additive effects to increase risk of T2DM (also associated with LDL lowering albeit with smaller effect than on CV risk).

In healthy, normolipidemic subjects, evolocumab decreased the concentration of atherogenic lipoproteins, particularly LDL, by accelerating their catabolism. These kinetic findings provide a metabolic basis for understanding the potential benefits of PCSK9 monoclonal antibodies incremental to statins in on-going clinical endpoint trials. In high-risk Korean patients with hypercholesterolemia on statin therapy, alirocumab markedly reduced LDL-C vs. placebo and was well tolerated over 52 weeks. The first large clinical trial to assess the CV outcomes of PCSK9 inhibition on a background of statin therapy showed that evolocumab significantly reduced the risk of CV events with no difference in the number of adverse events (including new-onset T2DM and neurocognitive events). However, a median follow-up period of 2.2 years is too short for safety issues, and more prolonged exposure to extremely low LDL-C levels could negatively affect new-onset T2DM and neurocognitive events via impaired cellular function.

Benefits and Harms of Statins Depend on Potency of Treatment

The previous meta-analysis demonstrated an association between the degree of LDL-C reduction and reduced risk of CV events. Indeed, the ideal therapy would simultaneously lower LDL-C to target levels while reducing the risk of T2DM and progression of existing T2DM instead of increasing it. One mechanism by which statins may increase the risk of T2DM is through a modest increase in body weight, increased IR and decreased β-cell function. Further, the physiological mechanisms evaluated in this study support our previous studies suggesting that the major cause of statin-induced T2DM is reduced insulin secretion and increased IR. Evidence from genetic analysis and RCTs suggests that the increased risk of T2DM noted with statins is at least partially explained by 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibition. In a stratified analysis of the JUPITER data, participants with ≥1 T2DM risk factor were at higher risk of incident T2DM than those without T2DM risk factors. By contrast, in individuals with no major T2DM risk factors, rosuvastatin treatment did not cause T2DM and reduced CV events by 52%, 13% more than in the former group. This may just be because it is easier to detect adverse metabolic actions in patients with more risk factors. Recent genetic studies clearly demonstrated this. PCSK9 inhibitors and statins use distinct mechanisms to lower LDL-C, the common downstream effect that is likely related to both protection against CVD and promotion of T2DM. In subjects with preexisting glucose intolerance, variants in both genes were also associated with independent and additive effects to increase risk of T2DM (also associated with LDL lowering albeit with smaller effect than on CV risk).

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These genotype-phenotype data strongly support the results of large clinical outcome studies demonstrating increased risk of T2DM with statin therapy. Moreover, an on-target mechanism of action is likely to promote T2DM given the genetic data. Although T2DM onset and progression related to statin use has not been demonstrated to increase CV events, long-term adverse effects may generate a relative increase in CV and all-cause morbidity or mortality when compared with equivalent lipid-lowering in the absence of adverse metabolic actions. It is likely that the previous large outcome studies of statin therapy underestimated the magnitude of metabolic risk because they did not have T2DM onset as a primary study outcome, and the patient population was different with less initial metabolic risks.

On the other hand, the Women’s Health Initiative study recruited 161,808 postmenopausal women aged 50–79 years and reported that statin use at baseline was associated with an increased risk of T2DM (multivariate-adjusted hazard ratio (HR), 1.48). Women may be more vulnerable than men to developing T2DM by statins. A recent meta-analysis included 59,744 participants (22,490 women, 37,254 men). Although statin treatment reduced the risk of total mortality, the risks of major coronary events and cerebrovascular events were not reduced by statin treatment in women without CVD. Although major adverse events and total cancer were not increased in either male or female patients taking statins, the stratified analysis by sex revealed a higher risk of development of T2DM in female patients (relative risk 1.50; 95% confidence interval 1.11–2.01).

Optimal Dose of Statins in Asian Patients

High-dose statin treatment should be avoided in the elderly, women, and Asian patients because the risk of statin-associated new-onset T2DM might be higher. Atorvastatin and rosuvastatin have been reported to increase IR during coronary bypass surgery in Japanese patients without T2DM. RCT studies have been performed in Caucasians primarily, except for the MEGA and Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) studies. The MEGA study performed in Japanese demonstrated similar reductions in the CV outcomes with a much lower dosage (mean dosage 19 mg) of pravastatin compared with Caucasians using...
40 mg of pravastatin.\textsuperscript{47,48} The JUPITER\textsuperscript{5,49} and HOPE-3\textsuperscript{50} trials evaluated clinical outcomes stratified according to race/ethnicity. In JUPITER, estimates were less precise, with no clear differences in more specific CV outcomes.\textsuperscript{49} Estimates for Asian race were not reported separately, because of a small sample. The HOPE-3 study examined 12,705 subjects with at least 1 known CV risk factor, but who had not been diagnosed with CVD (at intermediate risk). The predominant racial/ethnic group was Chinese (29\%), followed by Hispanic (27\%); whites accounted for 20\% of the study population. The HOPE-3 trial found no clear interaction between race/ethnicity and the effects of statins on composite CV events. A retrospective cohort study using National Periodic Health Examinations data showed that moderate-intensity pitavastatin 4 mg and high-intensity (optimal dose) statin ± ezetimibe combined with RAS blockade or PPARα agonist to reduce diabetogenic effect of statin.*

Table 2. Proposed Guideline to Maximize Cardiometabolic Benefits of Statins

<table>
<thead>
<tr>
<th>Primary prevention</th>
<th>Secondary prevention</th>
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<tr>
<td>Without risk factors* for diabetes: low-intensity low (for Asian) or moderate-intensity (optimal doses for Caucasian) statins alone</td>
<td>In acute coronary syndrome state: high-intensity statins such as atorvastatin 40–80 mg or rosuvastatin 20–40 mg ± ezetimibe/PCSK9 inhibitor/inclisiran because cardiovascular benefits of statins exceed diabetogenic or other risks</td>
</tr>
<tr>
<td>With risk factors for diabetes: low-intensity or moderate-intensity statin ± ezetimibe combined with RAS blockade or PPARα agonist to reduce diabetogenic effect of statin</td>
<td>In stable coronary artery disease: moderate-intensity (optimal dose) statin ± ezetimibe combined with RAS blockade or PPARα agonist</td>
</tr>
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*Impaired glucose tolerance, obesity, metabolic syndrome. PCSK9, proprotein convertase subtilisin/kexin type 9; PPARα, peroxisome proliferator-activated receptor α; RAS, renin-angiotensin system.

Although the benefit of statin treatment seems similar according to ethnicity, the optimal dose of statins would be lower in Asians because of biological and dietary differences, except for acute coronary syndrome (ACS), which requires potent and high-dose statins to prevent sudden cardiac death. Indeed, average lipid levels are much lower than in Asians than in Caucasians.\textsuperscript{21}

**Combined Statin Therapy to Optimize Simultaneous CV and Metabolic Benefits**

Although LDL-C lowering is of paramount important to reduce CV events, there is no definite cutoff margin for cost-effectively lowering LDL-C levels over a lifelong period. In the neonate, LDL-C levels are from 21 to 39 mg/dL.\textsuperscript{53} Cholesterol is a major constituent of the brain and eye lens and, thus, too low LDL-C levels may impair neurocognitive function, and the eye lens despite the reduction in CVD events. Some experts suggest 60 mg/dL would be ideal because that is required to maintain homeostasis; the European guideline has a target LDL-C <70 mg/dL.\textsuperscript{11} A recent study showed a monotonic relationship between achieved LDL-C and major CV outcomes down to LDL-C concentrations <0.2 mmol/L (7.7 mg/dL), and there were no safety concerns with very low LDL-C concentrations over a median of 2.2 years.\textsuperscript{48} However, patients who have achieved LDL-C levels below the currently recommended targets may still experience CV events, because of the residual risk such as IR and atherogenic dyslipidemia in subjects with metabolic syndrome.\textsuperscript{54}

Ezetimibe and PCSK9 inhibitors are promising lipid-lowering drugs. A recent study demonstrated that lowering LDL-C levels to 58 mg/dL with ezetimibe on simvastatin 40 mg significantly reduced the rates of major CV events without adverse effects, compared with simvastatin alone.\textsuperscript{55} Recent studies showed that LDL-C levels <25 mg/dL or <15 mg/dL on a PCSK9 inhibitor, alirocumab, were not associated with an increase in overall treatment-emergency adverse event rates or neurocognitive events, although cataract incidence increased 3-fold in the group achieving LDL-C levels <25 mg/dL.\textsuperscript{56} However, the follow-up period was not long enough for safety to be fully evaluated. The first large trial of evolocumab reported that inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL-C levels to a median of 30 mg/dL and reduced the risk of CV events.\textsuperscript{48} Although evolocumab was not correlated with reduced cognitive function over a median of 19 months,\textsuperscript{57} more prolonged exposure to extremely low LDL-C levels could cause neurocognitive dysfunction, cataracts and new-onset T2DM because it would impair cellular function, although these studies reported no incidence of T2DM.\textsuperscript{41,56-58}

Inclisiran, promising in cholesterol-lowering strategies, may be an alternative to statins and monoclonal antibodies.\textsuperscript{59} Inclisiran was found to lower PCSK9 and LDL-C levels among patients at high CV risk who had elevated LDL-C levels.\textsuperscript{40}

A recent study reported that heterozygous carriers of angiopoietin-like 3 (ANGPTL3) loss-of-function mutations showed a 34% reduction in the odds of coronary artery disease and that oligonucleotides targeting mouse ANGPTL3 retarded the progression of atherosclerosis by reducing atherogenic lipoproteins levels and increasing insulin sensitivity.\textsuperscript{61} Inactivating the mutations in ANGPTL4 inhibiting activation of lipoprotein lipase also had led to lower levels of triglycerides and a lower risk of CAD in carriers than in noncarriers.\textsuperscript{52} These studies are promising because oligonucleotide therapeutics, a new class of drugs that target RNA directly, may be alternatives...
to statins and monoclonal antibodies because of their potency, relatively infrequent administration requirement, cost, etc. However, the data caution that future outcome studies of oligonucleotide therapeutics should be designed for optimal detection of adverse metabolic actions in addition to CV events.  

Another recent study demonstrated that adding ezetimibe or PCSK9 monoclonal antibodies to maximally tolerated statin therapy may be cost-effective in very high-risk patients. Now, we should think about the cost-effectiveness. The PCSK9 inhibitors, alirocumab and evolocumab, are very expensive and would be unnecessary except some patients such as those with familial hypercholesterolemia, intolerance to statins, or in ACS. The benefit of evolocumab is consistent regardless of the intensity of statin therapy. When considering the independent and additive effects that increase the risk of T2DM with PCSK9 inhibitors and statins, PCSK9 inhibitors and low-intensity statin therapy may be better for both protection against CVD and new-onset T2DM, particularly in Asians. Otherwise, ezetimibe or renin-angiotensin-system (RAS) blockade combined with statins would be more cost-effective while endeavoring to control residual risk, because statins control less than 50% of CV events (Table 2).  

**Clinical Implication**

Treating moderate cholesterol elevations with low-dose statins reduces CVD by 35–40%. However, statin therapy alone dose-dependently causes IR and increases the risk of T2DM. Recent genetic studies showed on-target, not off-target effects of statins on the risk of T2DM. Furthermore, the effects of LDL-C-lowering genetic variants are independent and additive.  

Combination therapy with statins and other classes of drugs such as ezetimibe, RAS blockade, PCSK9 inhibitors, or inclisiran is a promising approach to maximizing therapeutic benefit while reducing inherent the metabolic risks of potent statins. For patients with ACS, high-intensity statins such as atorvastatin 40–80 mg or rosuvastatin 20–40 mg with or without ezetimibe/PCSK9 inhibitors or inclisiran are recommended because the effect of CV events is likely to be greater than the additional diabetogenic or other risks. If patients stabilize after 3 months or in patients with stable angina, moderate-intensity (optimal doses) statins with or without ezetimibe combined with RAS blockade or peroxisome proliferator-activated receptor α (PPARα) agonist are recommended. For the primary prevention of heart disease, if patients do not have risk factors for T2DM such as impaired glucose tolerance, obesity, or metabolic syndrome, low-intensity (for Asians) or moderate-intensity (optimal) (for Caucasians) statins alone is acceptable. However, if patients have risk factors for T2DM, we recommend low-intensity low or moderate-intensity statins (ezetimibe combined with RAS blockade or PPARα agonist) to reduce the diabetogenic effect of statins. This guideline to achieving the same target LDL-C level might enable the beneficial CV effects of lowering LDL-C while minimizing any adverse outcomes and overcoming residual risk of high-intensity statin treatment (Table 2).  

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**Conflict of Interest**

K.K.K. holds a certificate of patent, 10-1579656 (pravastatin+valsartan).

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