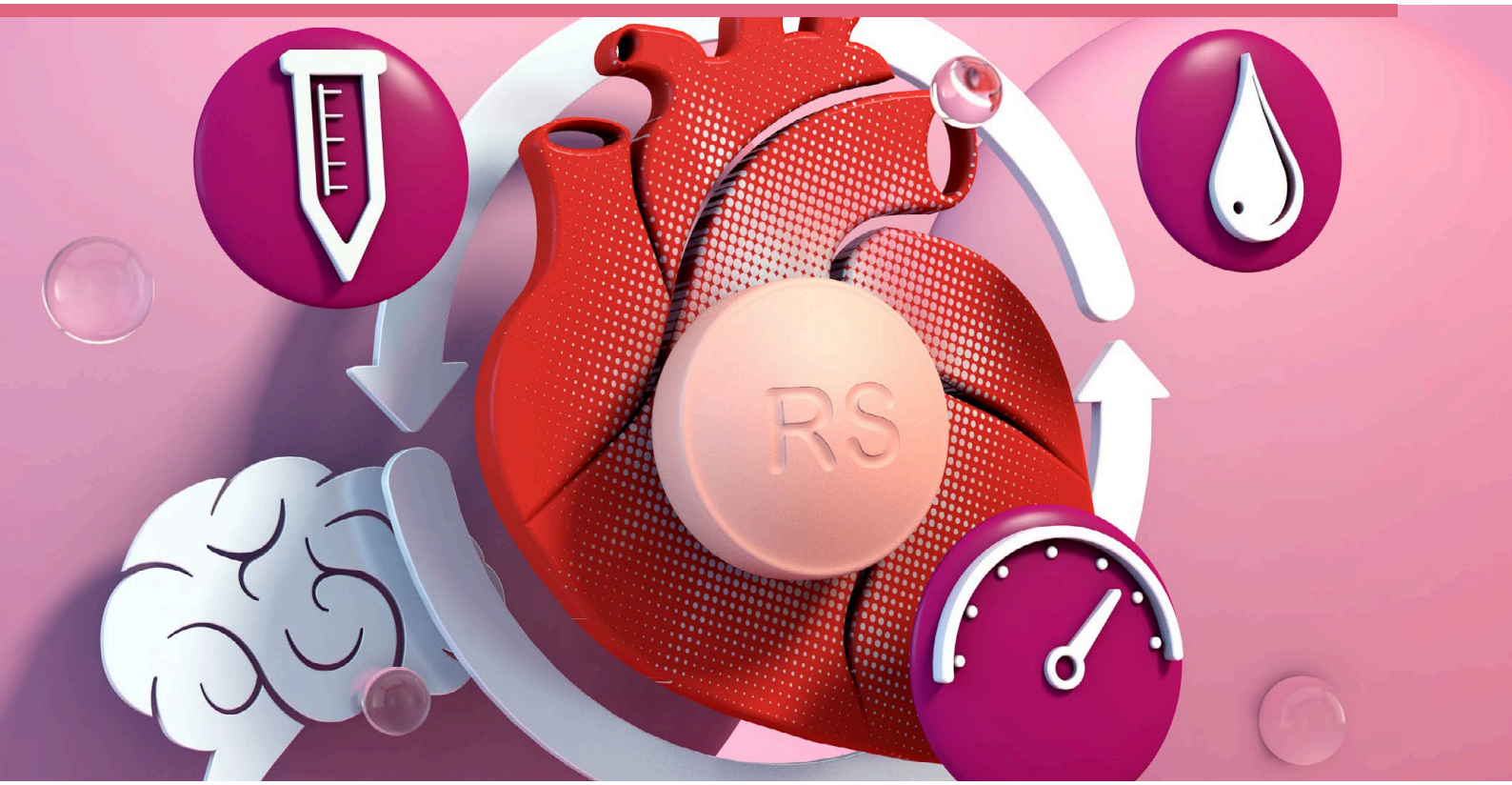

Rosuvastatin: another option to lower cardiovascular disease risk

As of 1 December, 2021, rosuvastatin is funded with Special Authority approval in New Zealand. Rosuvastatin is a more potent statin than other currently funded options. It can be considered for patients with a high risk of cardiovascular disease who have elevated lipid levels despite treatment with other statins. Rosuvastatin may also be considered as a first-line treatment for Māori and Pacific peoples.

KEY PRACTICE POINTS

- Rosuvastatin is funded, with Special Authority approval, for patients who have not met lipid reduction targets with atorvastatin or simvastatin
- Rosuvastatin has a higher potency than other funded statins, with a similar adverse effect profile
- Atorvastatin remains the first-line treatment for most patients
- Rosuvastatin can be prescribed as a first-line treatment for Māori and Pacific peoples who are at increased risk of CVD
- Request liver function tests before initiating rosuvastatin, and creatinine kinase levels in selected patients
- Rosuvastatin is contraindicated in people who have active liver disease
- Higher doses of rosuvastatin (≥ 40 mg) are contraindicated in people with risk factors for, or a history of, myopathy or rhabdomyolysis
- Lower rosuvastatin doses are recommended in older people and people of Asian ethnicity

Rosuvastatin: a more potent statin

HMG-CoA reductase inhibitors, more often referred to as statins, are considered the first-line pharmacological intervention for lipid management in New Zealand.[1] Each 1.0 mmol/L reduction in LDL cholesterol (LDL-C) from a statin is associated with a 25% relative reduction in cardiovascular disease (CVD) risk over five years.[1]

Rosuvastatin has been an approved medicine in New Zealand since 2013,[2] but has not been funded, limiting access for most people. Previously, only pravastatin, simvastatin and atorvastatin were funded in New Zealand.[3]

Rosuvastatin is rapidly absorbed, has a half-life of 20 hours[4] and is more potent than other statins (Table 1).[1] For example, while rosuvastatin and atorvastatin produce similar reductions in LDL-C, rosuvastatin is approximately three to four times more potent,[1,4] with a similar adverse effect profile.[5,6]

Cardiovascular disease risk management

All patients, regardless of cardiovascular risk, should be encouraged to follow a healthy diet, take part in regular physical exercise and maintain an optimal weight.[1] After lifestyle modifications, a patient's cardiovascular risk determines their treatment:[1]

- Pharmacological intervention is recommended in patients with an estimated five-year CVD risk of ≥ 15% over the next five years or with a total cholesterol to high-density lipoprotein (HDL) cholesterol (TC/HDL-C) ratio of eight or higher; with an LDL-C treatment target of < 1.4 mmol/L
- Pharmacological intervention can be considered in patients with an estimated five-year CVD risk of 5 – 15%, after first discussing the benefits and risks of treatment
- Lifestyle modifications are usually sufficient in patients with an estimated five-year CVD risk of < 5%, and pharmacological intervention is not generally recommended

For further information on the role of lipid management in cardiovascular disease, see: **bpac.org.nz/2018/lipids.aspx**

Rosuvastatin funded with Special Authority

From 1 December, 2021, rosuvastatin has been funded for eligible patients.[7] This provides another option for patients who are at high risk of cardiovascular disease and have not managed to reduce their lipid levels with the currently funded medicines.[7]

The Special Authority eligibility criteria also allows access to rosuvastatin as a first-line treatment for Māori and Pacific peoples. Prioritising this patient group, who are more likely to develop CVD at a younger age and experience higher CVD mortality than non-Māori and non-Pacific peoples,[8–10] aims to reduce inequalities in CVD health outcomes.

Any health practitioner (including nurse practitioners and pharmacist prescribers, working within their scope), can apply for a Special Authority for a patient for rosuvastatin and renewals are not required (unless notified).[7]

N.B. Māori and Pacific peoples with type 2 diabetes have also been specifically identified within Special Authority criteria for empagliflozin and GLP-1 receptor agonist treatment.

For further information on empagliflozin and GLP-1 receptor agonists, see: **bpac.org.nz/2021/diabetes.aspx**

Initiating funded treatment

Four key groups of people are eligible for funded treatment with rosuvastatin under the Special Authority criteria:[7]

1. **Cardiovascular disease risk:**

a. Māori and Pacific peoples at risk of CVD are eligible for rosuvastatin as a first-line treatment; or

b. Patient has a 15% or greater CVD risk over the next five years and has already been prescribed the maximum tolerated dose of atorvastatin or simvastatin and has not lowered LDL cholesterol below 1.8 mmol/L

Table 1. Statin potency – approximate equivalence, adapted from Cardiovascular Disease Risk Assessment and Management for Primary Care, 2018.[1]

Potency	Pravastatin	Simvastatin	Atorvastatin	Rosuvastatin	LDL-C reduction
Low	20 mg	10 mg			**30%**
Medium	40 mg	20 mg	10 mg		**38%**
Medium	80 mg	40 mg	20 mg	5 mg	**41%**
High		80 mg	40 mg	10 mg	**47%**
High			80 mg	20 mg	**55%**
Very high				40 mg	**63%**

For further information on calculating cardiovascular disease risk, see: **www.nzssd.org.nz/cvd/**

2. Familial hypercholesterolaemia:

a. Patient has been diagnosed with familial hypercholesterolaemia, defined as a score greater than or equal to six using the Dutch Lipid Clinic Network criteria*; and

b. Has already been prescribed the maximum tolerated dose of atorvastatin or simvastatin and has not lowered their LDL cholesterol below 1.8 mmol/L

* For further information on the Dutch Lipid Clinic Network, see: **www.athero.org.au/fh/wp-content/uploads/Dutch-Lipid-Clinic-Network-Score2.pdf**

3. Established cardiovascular disease:

a. Patient has either:

i. Diagnosed coronary artery disease; or

ii. Diagnosed peripheral artery disease; or

iii. Experienced an ischaemic stroke; and

b. Has already been prescribed the maximum tolerated dose of atorvastatin or simvastatin and has not lowered their LDL cholesterol below 1.4 mmol/L

4. Recurrent major cardiovascular events:

a. Patient has experienced a recurrent major cardiovascular event (defined as an ischaemic stroke, myocardial infarction, coronary revascularisation or admitted to hospital for unstable angina), in the last two years; and

b. Has already been prescribed the maximum tolerated dose of atorvastatin or simvastatin and has not lowered their LDL cholesterol below 1.0 mmol/L

LDL-C target is < 1.4 mmol/L in people at high risk

The LDL-C eligibility criteria for initiating rosuvastatin in different patient groups is summarised in Table 2. Although these are the criteria for accessing funded treatment, it is important to note that the New Zealand Regional Committee of the Cardiac Society of Australia and New Zealand recommend that people with a five-year CVD risk of ≥ 15% should aim for an LDL-C treatment target of < 1.4 mmol/L. For example, a person with a CVD risk of ≥ 15% who has an LDL-C level of 1.7 mmol/L would not be eligible for funded treatment with rosuvastatin (unless they met other criteria), but would still be recommended to reduce their LDL-C level to below 1.4 mmol/L.

Read the statement here: **cardiacsociety.org.nz/lipid-treatment-targets-in-individuals-at-high-cardiovascular-risk/**

Prescribing rosuvastatin

Rosuvastatin is prescribed once daily and can be taken at any time of day (Table 3). Patients should have their LDL-C measured every 6 – 12 months, and after the appropriate target is reached, yearly monitoring is sufficient.[1]

Contraindications to rosuvastatin treatment

Rosuvastatin is contraindicated in people who have active liver disease or persistently raised transaminases (greater than three times upper limit of normal).*[3] Liver function should be assessed before initiating rosuvastatin and then periodically during treatment (depending on risk factors).[3, 11, 13] Caution is recommended when prescribing rosuvastatin to patients with a history of excessive alcohol intake or liver disease, and regular monitoring of liver function is advised in these patients (see below).[3]

* Raised transaminases do not necessarily preclude a patient from receiving rosuvastatin, but do not prescribe if transaminases are greater than three times upper limit of normal[3, 11]

Table 2. LDL-C level eligibility for rosuvastatin funding.[7]

	Minimum eligible LDL-C level
Māori or Pacific peoples	
High risk of cardiovascular disease	N/A
Patients who have received maximum tolerated atorvastatin and/or simvastatin dose	
Calculated risk of CVD at least 15% over five years	1.8 mmol/L
Familial hypercholesterolaemia	1.8 mmol/L
Established cardiovascular disease	1.4 mmol/L
Recurrent major cardiovascular events	1.0 mmol/L

Rosuvastatin is contraindicated in the first trimester of pregnancy.[3] An increased risk of miscarriage has been reported in patients exposed to statins during pregnancy, however, there has been no association with increased rates of birth defects.[14] Due to a lack of reported data on rosuvastatin in human pregnancy exposures, **it is recommended that rosuvastatin is avoided in all stages of pregnancy**.[2,3] Patients of child-bearing potential should use adequate contraception during treatment and for one month after if treatment stops.[3] Patients who become pregnant while taking rosuvastatin should stop taking the medicine immediately.[14]

Doses of 40 mg rosuvastatin are contraindicated in people with risk factors for, or a history of, myopathy or rhabdomyolysis:[3]

- History of statin-associated myopathy
- Hereditary muscular disorders
- Hypothyroidism
- Creatinine clearance < 30 mL/min
- Asian ethnicity (including people from the Indian subcontinent, Chinese, Korean, Vietnamese, Filipino and Japanese)
- Excessive alcohol consumption
- Concurrent use of fibrates

For further information on assessing alcohol consumption, see: **bpac.org.nz/2018/alcohol.aspx**

Table 3. Key rosuvastatin prescribing information.[3]

Prevention of cardiovascular disease	■ Initiate at 20 mg once daily
Hypercholesterolaemia	■ Initiate at 10 mg once daily and increase after two to four weeks to 20 mg once daily, if required ■ For severe hypercholesterolaemia, consider 20 mg initial dose and increase up to 40 mg, if required
Homozygous familial hypercholesterolaemia	■ Initiate at 20 mg once daily and increase after two to four weeks to 40 mg once daily, if required ■ If also prescribed a fibrate*, initiate at 5 mg once daily, increasing to a maximum 20 mg once daily, if required
Before starting medicine	■ Assess liver function in all patients – do not prescribe if serum transaminases are greater than three times upper limit of normal ■ Measure CK levels in patients with risk factors for myopathy or rhabdomyolysis – do not prescribe if CK levels are greater than five times the upper limit of normal ■ Assess HbA_{1c} in patients at high risk of diabetes
Ongoing monitoring	■ Assess liver function periodically in all patients (depending on risk factors) – halt treatment if serum transaminases are greater than three times upper limit of normal ■ Measure CK levels in patients who develop muscle pain or weakness – reduce dose if CK levels are 3 – 10 times the upper limit of normal and halt treatment if CK levels are greater than 10 times upper limit of normal ■ Assess HbA_{1c} at three months in patients at high risk of diabetes and then as clinically indicated ■ Assess renal function periodically in all patients taking 40 mg rosuvastatin (depending on risk factors)
Notes	■ If risk factors for myopathy or rhabdomyolysis, or Asian ethnicity†, initiate at 5 mg once daily, increasing to a maximum 20 mg daily, if required ■ If severe hepatic impairment, use with caution and initiate at 10 mg, once daily ■ If creatinine clearance < 30 mL/min, do not exceed 10 mg once daily

N.B. Rosuvastatin is available in 5 mg, 10 mg, 20 mg and 40 mg tablets.[3]

* Fibrates are no longer routinely recommended for lipid lowering treatment.[11] For further information, see: **bpac.org.nz/2021/statins.aspx**

† People of Asian ethnicity (including people from the Indian subcontinent, Chinese, Korean, Vietnamese, Filipino and Japanese) require a lower dose of rosuvastatin compared to other ethnicities as pharmacokinetic studies have demonstrated a reduced oral clearance, increasing the risk for elevated serum levels and adverse effects[2,3,12]

Cautions to rosuvastatin treatment

Increased risk of diabetes in some patients. There is an association between patients taking rosuvastatin and developing type 2 diabetes (also see: "Adverse effects").[2] This generally applies to patients already at an increased risk of developing type 2 diabetes before starting statin treatment (e.g. older people, elevated HbA_{1c}, increased BMI).[2, 3, 15] Even with an increased risk of developing type 2 diabetes and increased CVD risk with statin-induced diabetes), the evidence does not support withholding a statin, as the expected decrease in major cardiovascular events outweighs the risks.[5, 15] Patients at higher risk of developing type 2 diabetes should have HbA_{1c} checked at three months and then as clinically indicated.[1, 3]

Interactions with other medicines

Rosuvastatin has fewer medicine interactions than the other funded statins. Atorvastatin and simvastatin are metabolised by CYP3A4, which is involved in a number of medicines interactions (e.g. macrolide antibiotics and azole antifungals are potent CYP3A4 inhibitors, leading to increased plasma levels of statins),[3, 16, 17] whereas 90% of the rosuvastatin dose is excreted unchanged and there is only partial metabolism by CYP2C9.*[6, 17]

Rhabdomyolysis, a serious outcome of statin-medicine interactions, has been reported in patients taking erythromycin and either atorvastatin or simvastatin, but the interaction is not clinically relevant for rosuvastatin (although rhabdomyolysis is a rare adverse effect of statins in general – see below).[3]

Care should still be taken when prescribing rosuvastatin alongside ciclosporin and clopidogrel due to the risk of elevated rosuvastatin levels and rhabdomyolysis.[3]

To prevent decreased rosuvastatin exposure, antacids (e.g. aluminium/magnesium hydroxide) should be taken two hours apart from the rosuvastatin dose.[3]

* Pravastatin only undergoes minor metabolism by CYP3A4, and similarly has fewer medicines interactions with potent CYP3A4 inhibitors [18]

Check for medicine interactions prior to prescribing rosuvastatin to reduce the risk of adverse effects: **www.nzf.org.nz/interactions/stockleys/of/10227401000116101**

Adverse effects of rosuvastatin

Rosuvastatin, like other statins, is well tolerated.[2] Myopathy, an increased risk of the development of type 2 diabetes and an increase in haemorrhagic stroke (the decreased risk of ischaemic stroke outweighs this) have all been linked to statin treatment.[15] Depending on patient co-morbidities and the intensity of the statin, rhabdomyolysis can develop.[19]

For further information on adverse effects of rosuvastatin, see: **www.nzf.org.nz/nzf_1616**

Early clinical trials reported small numbers of patients taking rosuvastatin developed myalgia, myopathy and rhabdomyolysis.[2] While myalgia is commonly reported in patients taking statins, significant myopathy, defined as rhabdomyolysis or creatine kinase (CK) greater than 10 times the upper limit of normal, is rare.[3] A 2014 study showed a statistically significant increase in the risk of clinically relevant myopathy in people receiving 20 mg and 40 mg rosuvastatin, compared to other available statins.[20]

Therefore, before starting rosuvastatin, it is important to **measure CK levels in patients with risk factors** for myopathy or rhabdomyolysis (also see: "Contraindications to rosuvastatin treatment").[3, 11] It is not recommended to prescribe rosuvastatin if CK levels are greater than five times the upper limit of normal.[3, 11] Ongoing CK monitoring is not usually required, unless patients report muscle pain and weakness.[1, 3] In this situation, measure CK and if:[1, 3]

- CK levels are from three-to-ten times upper limit of normal – reduce dose and reassess weekly
- CK levels are greater than ten times upper limit of normal – discontinue rosuvastatin

New onset type 2 diabetes is more commonly seen in older people on higher-dose statins.[15] One study found that patients with at least one risk factor for developing type 2 diabetes, and who were prescribed 20 mg rosuvastatin, were at greater risk (28%) of developing diabetes, compared to placebo.[21]Rosuvastatin has been shown to increase HbA_{1c} and insulin resistance,[22] and is associated with an increase in the rate of onset of type 2 diabetes, compared to atorvastatin or pravastatin.[19, 23] This is thought to be due to the intensity of the statin treatment, and not differences in pharmacokinetic properties.[24]

Switching statins

Clinical guidelines regarding switching from another statin to rosuvastatin are lacking. A reasonable approach is to stop the original statin and start rosuvastatin the next day. If a patient does not tolerate rosuvastatin treatment, consider reducing the dose or switching to another statin.[3] Potency of the statin (Table 1) and history of adverse effects should be considered if switching medicines. The new statin dose should be titrated up until the target LDL-C is reached.

For further information on managing intolerance to statin treatment, see: **www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/08/Statin-Intolerance-Pathway-NEW.pdf**

For further information on the role of statins in lipid management, see: **bpac.org.nz/2021/statins.aspx**

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References

1. Ministry of Health NZ. Cardiovascular disease risk assessment and management for primary care. Available from: https://www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care (Accessed Jan, 2022).
2. Viatris Ltd. New Zealand Datasheet: Rosuvastatin Viatris. 2021. Available from: https://www.medsafe.govt.nz/profs/datasheet/r/rosuvastatinviatristab.pdf (Accessed Jan, 2022).
3. New Zealand Formulary (NZF). NZF v114. Available from: www.nzf.org.nz (Accessed Jan, 2022).
4. Adams SP, Sekhon SS, Wright JM. Rosuvastatin for lowering lipids. Cochrane Database Syst Rev 2014; doi:10.1002/14651858.CD010254.pub2.
5. Cortese F, Gesualdo M, Cortese A, et al. Rosuvastatin: Beyond the cholesterol-lowering effect. Pharmacol Res 2016;107:1–18. doi:10.1016/j.phrs.2016.02.012.
6. Luvai A, Mbagaya W, Hall AS, et al. Rosuvastatin: A review of the pharmacology and clinical effectiveness in cardiovascular disease. Clin Med Insights Cardiol 2012;6:CMC.S4324. doi:10.4137/CMC.S4324.
7. PHARMAC. Decision to fund rosuvastatin for people with high cholesterol. PHARMAC 2021. Available from: https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/2021-08-17-decision-rosuvastatin/(Accessed Jan, 2022).
8. Beadel H, Halim A, Bridgford P, et al. Lipid monitoring in a community cohort of people taking statins: who is tested and is testing associated with subsequent alteration in therapy? N Z Med J 2020;133:54–63.
9. Ministry of Health NZ. Ngā mana hauora tūtohu: Health status indicators, Cardiovascular disease. Available from: www.health.govt.nz/our-work/populations/maori-health/tatau-kahukura-maori-health-statistics/nga-mana-hauora-tutohu-health-status-indicators/cardiovascular-disease (Accessed Jan, 2022).
10. Ministry of Health NZ. Pacific people's health. Available from: www.health.govt.nz/our-work/populations/pacific-health/pacific-peoples-health (Accessed Jan, 2022).
11. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction including lipid modification. Available from: https://www.nice.org.uk/guidance/cg181 (Accessed Dec, 2020).
12. Tzeng T-B, Schneck DW, Birmingham BK, et al. Population pharmacokinetics of rosuvastatin: implications of renal impairment, race, and dyslipidaemia. Curr Med Res Opin 2008;24:2575–85. doi:10.1185/03007990802312807.
13. British National Formulary (BNF). BNF 79. London: BMJ Publishing Group and Royal Pharmaceutical Society of Great Britain 2020.
14. Pang J, Chan DC, Watts GF. The knowns and unknowns of contemporary statin therapy for familial hypercholesterolemia. Curr Atheroscler Rep 2020;22:64. doi:10.1007/s11883-020-00884-2.
15. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. The Lancet 2016;388:2532–61. doi:10.1016/S0140-6736(16)31357-5.
16. Abu Mellal A, Hussain N, Said AS. The clinical significance of statins-macrolides interaction: comprehensive review of in vivo studies, case reports, and population studies. Ther Clin Risk Manag 2019;15:921–36. doi:10.2147/TCRM.S214938.
17. Medsafe. Statins and CYP interactions. Prescriber Update. 2014. Available from: https://www.medsafe.govt.nz/profs/PUArticles/March2014StatinsAndCYPInteractions.htm# (Accessed Jan, 2022).
18. Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. Expert Opin Drug Metab Toxicol 2020;16:809–22. doi:10.1080/17425255.2020.1801634.
19. Ward NC, Watts GF, Eckel RH. Statin toxicity: Mechanistic insights and clinical implications. Circ Res 2019;124:328–50. doi:10.1161/CIRCRESAHA.118.312782.
20. van Staa TP, Carr DF, O'Meara H, et al. Predictors and outcomes of increases in creatine phosphokinase concentrations or rhabdomyolysis risk during statin treatment: Statins and muscle toxicity. Br J Clin Pharmacol 2014;78:649–59. doi:10.1111/bcp.12367.
21. Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. The Lancet 2012;380:565–71. doi:10.1016/S0140-6736(12)61190-8.
22. Koh KK, Quon MJ, Sakuma I, et al. Differential metabolic effects of rosuvastatin and pravastatin in hypercholesterolemic patients. Int J Cardiol 2013;166:509–15. doi:10.1016/j.ijcard.2011.11.028.
23. Navarese EP, Buffon A, Andreotti F, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol 2013;111:1123–30. doi:10.1016/j.amjcard.2012.12.037.
24. Benes LB, Bassi NS, Davidson MH. The risk of hepatotoxicity, new onset diabetes and rhabdomyolysis in the era of high-intensity statin therapy: does statin type matter? Prog Cardiovasc Dis 2016;59:145–52. doi:10.1016/j.pcad.2016.08.001.

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