The maximum dose of atorvastatin and simvastatin as well as rosuvastatin should be restricted in East Asians

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To the Editor—Statins are very safe medications when used in doses appropriate for the individual, but the letter from ML Tse highlights the risk of rhabdomyolysis with rosuvastatin 40 mg in Chinese patients.[1] It was known at the time of first registration of rosuvastatin in 2003 that plasma levels were twice as high in East Asians (Chinese and Japanese) compared with Caucasians. As 40 mg is the maximum dose of rosuvastatin approved in Western countries, it would seem appropriate to restrict the maximum dose to 20 mg in East Asians. This has been adopted in China, Korea, and Japan.

Plasma levels of atorvastatin and simvastatin acid, the active form of simvastatin, are also higher in Chinese and Japanese subjects compared with Caucasians.[2] The maximum dose of atorvastatin approved in Japan is 40 mg,[3] and the 2023 Chinese guideline for lipid management contains the comment 'Atorvastatin 80 mg is inexperienced in China, please use with caution.'[4]

The maximum approved or recommended daily dose of simvastatin is 20 mg in Japan and 40 mg in Korea and China. The Clinical Pharmacogenetics Implementation Consortium provides a guideline for genetic testing related to statin myopathy,[5] and since 2012 they have recommended that the dose of simvastatin be restricted to 20 mg in individuals with the common c.521T>C variant (rs4149056) in the *SLCO1B1* gene that encodes the OATP1B1 transporter. Considering this variant occurs in 11% to 16% of East Asians, it would seem wise to restrict the dose of simvastatin to 20 mg in the absence of genetic testing.

The Clinical Pharmacogenetics Implementation Consortium guideline applies to all ethnic groups. The relative risk of myopathy was 2.6 per copy of the *SLCO1B1* 521C variant in the Heart Protection Study with simvastatin 40 mg.[6] The increased risk of myopathy in Chinese patients was seen in the HPS2-THRIVE trial (Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events) where the combination of definite myopathy and incipient myopathy was about 10 times higher in China than in Europe (0.66% per year vs 0.07% per year; P<0.001) in participants taking simvastatin 40 mg in combination with extended-release niacin 2 g plus laropiprant 40 mg daily.[7] This was probably due to an unexpected pharmacokinetic interaction between simvastatin and niacin.

In 2019, we reported the case of a 69-year-old Chinese male diabetic who had taken simvastatin 40 mg for 10 years and developed rhabdomyolysis, possibly related to unexpected drug interactions with *Stevia rebaudiana* and/or linagliptin.[8] He was a carrier of one copy of *SLCO1B1* 521C and two copies of the C421>A variant of the adenosine triphosphate–binding cassette transporter G2 gene. That variant is more frequent in Chinese subjects. This illustrates that despite apparent long-term safe administration of simvastatin, it needs only an unpredicted drug-drug or herb-drug interaction or the gradual deterioration in renal function with age, which is more rapid in diabetics, to tip the balance and result in life-threatening toxicity in susceptible patients.

Author contributions

Both authors contributed to the concept or design, acquisition of data, analysis or interpretation of data, drafting of the letter, and critical revision of the letter for important intellectual content. Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

Both authors have disclosed no conflicts of interest.

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Answers to CME Programme
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Hong Kong Med J 2024;30:10-5

I. Non–vitamin K oral anticoagulants versus warfarin for the treatment of left ventricular thrombus

A	1. True	2. False	3. True	4. False	5. False
B	1. True	2. True	3. False	4. True	5. True

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II. COVID-19 vaccination and transmission patterns among pregnant and postnatal women during the fifth wave of COVID-19 in a tertiary hospital in Hong Kong

A	1. True	2. True	3. False	4. False	5. True
B	1. True	2. False	3. True	4. False	5. False