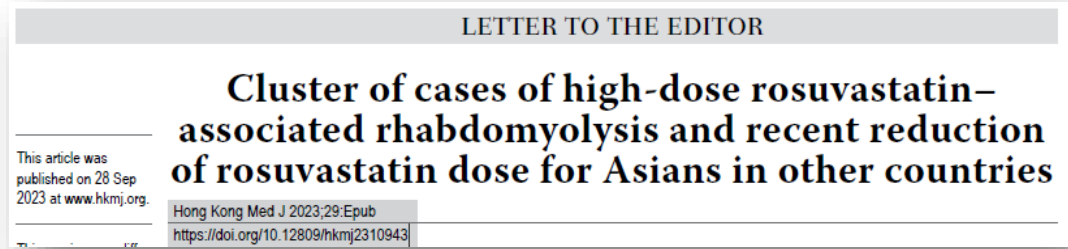


Safety update with high dose Rosuvastatin

Hospital Authority (HA), Hong Kong

23 October 2023

Background



- From July 2022 to April 2023, 6 cases of severe rhabdomyolysis in Chinese patients on high dose rosuvastatin (≥ 40 mg daily) were reported
Hong Kong Med J 2023;29:Epub
<https://doi.org/10.12809/hkmj2310943>
- Reported incidence rate of statin-associated rhabdomyolysis: 0.44 per 10,000 person-years
Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004;
- Being prescribed the same dose, Chinese had a plasma rosuvastatin level 2.3 times of White ethnic group
Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005
- Product inserts of Crestor (rosuvastatin calcium) were revised in 2022 in the United Kingdom, Australia and Canada
 - Asian ethnicity was a contraindication for prescription of 40 mg per day

Background

- In March 2023, HA received notification from the supplier of Rosuvastatin for update of product information

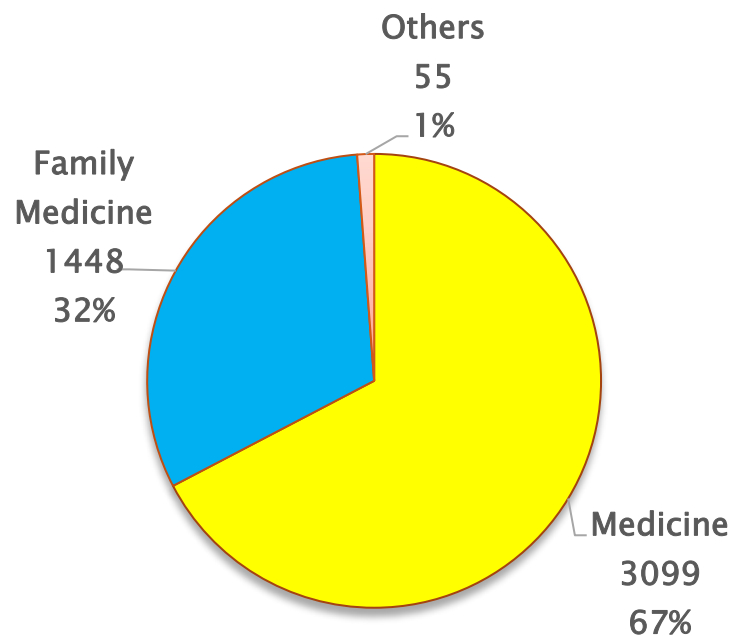
CONTRAINDICATIONS

• The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy rhabdomyolysis. Such factors include:

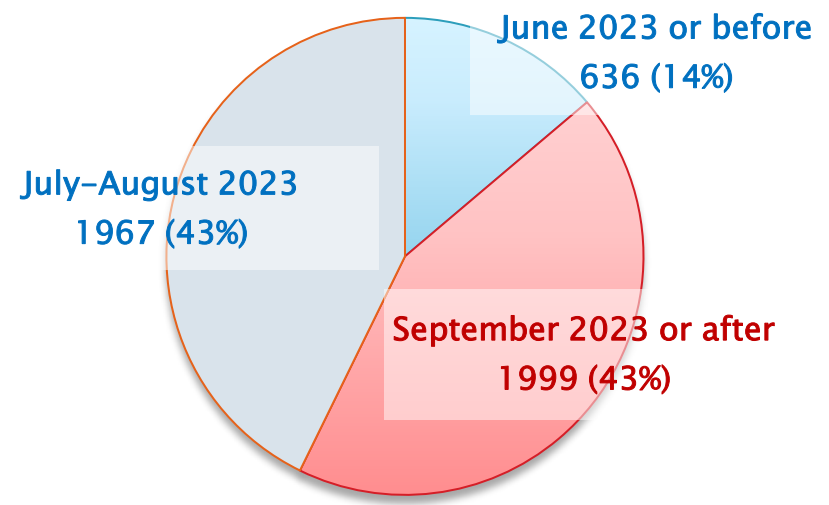
- Asian patients
- moderate renal impairment (creatinine clearance <60ml/min)
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in plasma levels may occur
- concomitant use of fibrates.

Situation of high dose Rosuvastatin in HA

- 100,316 out-patient headcount with dispensing record of Rosuvastatin in HA between July 2022 and June 2023
 - **4,602 (4.6%)** with daily dose ≥ 40 mg in latest record




Prescribing specialty



End date of last dispensing record

Consultation and recommendation

- Consulted expert advice from cardiologists and endocrinologists
- Deliberated in HA Medication Safety Committee (MSC) and Drug Management Committee (DMC)
- Public article in Medication Safety Bulletin issued in May 2023 on safety information update for Rosuvastatin
- A meeting was convened in June 2023 by MSC Chairperson involving clinical experts and HA Head Office representatives to formulate safety measures



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Safety information update for Rosuvastatin

HMG-CoA reductase inhibitors, also known as statins, are cholesterol-lowering medications used to reduce the risk of developing cardiovascular diseases.

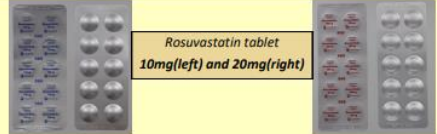
Statins can cause rare side effects on muscle (also known as myopathy), including muscle weakness, inflammation and damage. Intense pain could be a symptom of rhabdomyolysis, a rare condition that involves the breakdown of muscle cells.

Examples of signs and symptoms of rhabdomyolysis include:

- ※ Muscle weakness
- ※ Muscle pain
- ※ Elevated serum creatine kinase
- ※ Muscle swelling
- ※ Dark urine
- ※ Acute renal failure

There were recent reports of adverse drug reaction (ADR) related to statin-induced rhabdomyolysis in Asian patients on high dose of rosuvastatin (daily dose 40mg or above). The manufacturer of rosuvastatin products being used in HA also updated the Product Information on contraindications:

- **The 40mg dose is contraindicated in patients with pre-disposing factors for myopathy rhabdomyolysis. Such factors include:**
 - Asian patients
 - moderate renal impairment (creatinine clearance <60ml/min)
 - hypothyroidism
 - personal or family history of hereditary muscular disorders
 - previous history of muscular toxicity with another HMG-CoA reductase inhibitors or fibrate
 - alcohol abuse
 - situations where an increase in plasma levels may occur
 - concomitant use of fibrates.



Rosuvastatin tablet
10mg(left) and 20mg(right)

Advice on safe medication use:

Not everyone will experience side effects after using the medications. Their severity also differs among individuals. Please consult advice from doctor or pharmacist if the side effects persist or worsen. Do not stop using the medications or change the dose/frequency unless directed by doctor.

For patients taking statins, please seek medical advice if there is any unexplained muscle pain or weakness, loss of appetite, nausea, vomiting, dark urine, etc.

Management of Patients on high dose Rosuvastatin

Safety measures implemented in July 2023:

- **(1) The patient clinical management guideline has been updated**

Recommended Patient Clinical Management

Patients receiving rosuvastatin 40mg or above daily :

1. For those patient NOT receiving ezetimibe, it is suggested to reduce rosuvastatin dose to 20mg daily and add ezetimibe 10mg daily.
2. For those patients who are already receiving ezetimibe
 - If the patient has no documented contraindication / not ever received atorvastatin 80mg daily, it is suggested to switch rosuvastatin to atorvastatin 80mg daily.
(Please remind patient that there may be risk with high dose atorvastatin but the risk is not well described as high dose rosuvastatin in Asian patients)
 - If the patient has contraindication to atorvastatin 80mg daily or documented failure to achieve LDL goal with atorvastatin 80mg, it is suggested to switch rosuvastatin to PCSK9 inhibitors (Alirocumab or Evolocumab) or Inclisiran if clinically indicated.

****Always check and reinforce dietary and drug compliance***

****Recheck lipid profile after dosage adjustment, reassess the risk and whether LDL goal can be achieved***

Note: PCSK9 inhibitors (Alirocumab or Evolocumab) or Inclisiran should be provided to patients if there is no suitable alternative treatment. Impact on the drug budget utilisation from this exercise would be monitored and followed up at HAHO level.

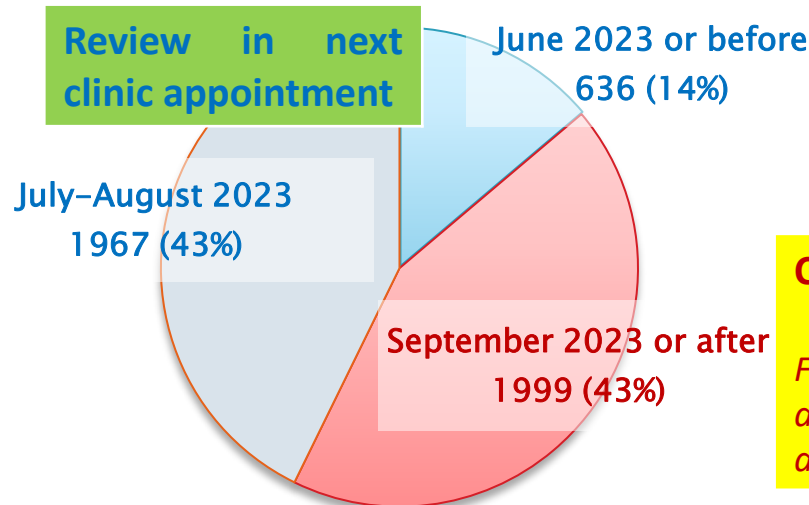
Management of Patients on high dose Rosuvastatin

Safety measures implemented in July 2023:

- **(2) Patient list on high dose rosuvastatin was distributed to corresponding hospitals and clinics for necessary follow-up**

- Patients on rosuvastatin daily dose > 40 mg: Contact for earlier appointment

- Patients on rosuvastatin daily dose = 40 mg: Review based on end date of on-hand drug



Contact for earlier appointment

For patients who cannot be contacted, a letter was sent to ask for appointment ASAP

End date of last dispensing record

Management of Patients on high dose Rosuvastatin

Safety measures implemented in July 2023:


- **(3) Pharmacy to clarify with the prescriber when high dose rosuvastatin (daily dose 40mg or above) is prescribed**
- **(4) Explore electronic system enhancement on dose-specific checking in drug order entry**

The screenshot shows a web-based medical interface with a blue header bar containing navigation tabs (File, 1. Clinical, 2. Investigation, 3. Enquiry, 4. Booking, 5. DT, 6. Report, 7. Doc./Print, 8. Other System, 9. Info., 0. Admin.) and a search bar. Below the header is a toolbar with various icons for functions like Logoff, Close, PSP, Doc/Px, AH Record, Rx Request, Disc Sum, Letter/Doc, Rx, Lab Result, ePR, Endoscopy, OT Record, IPMOE, Pre/Plan Note, Case/Inbox, Album, Case/Recruit, Cancer Note, and Next Patient. The main content area is titled 'Clinical Intervention' and features a prominent red banner with the text 'CAUTION for ROSUVASTATIN CALCIUM TABLET'. Below the banner, a white box contains the following text: 'Rosuvastatin dose 40mg or above daily is contraindicated for adults patients of Asian origin and may increase the risk of myopathy or rhabdomyolysis. Please consider to edit the prescription.' To the left of this box, there is a sidebar with patient information: 'Patient-specific Func', 'F 23y DOB:', 'Discharge Prescripti', 'Drug Name', and 'Prescribed Item(s)' with a list item '1. RO ora'. To the right of the main box, there are buttons for 'All Change', 'Remove', 'Edit', 'Save and Print', and 'Delete Order'. At the bottom of the main box, there are buttons for 'View Supplementary Information', 'Proceed Prescription', and 'Edit prescription'. Below the screenshot, two yellow callout boxes provide instructions: 'Save order after clicking "Proceed Prescription"' and 'Back to current Rx after clicking "Edit Prescription"'. The browser's address bar shows 'HA CMS | Lau, Su Man | VH | MED - Internet Explorer'.

Post-implementation monitoring

- Out-patient headcount with daily dose of Rosuvastatin ≥ 40 mg

| Month | Patient Count | |
|----------------|-----------------|------------------------------|
| | On Rosuvastatin | With daily dose ≥ 40 mg |
| February 2023 | 21,414 | 1,187 (5.5%) |
| March 2023 | 27,745 | 1,428 (5.2%) |
| August 2023 | 26,982 | 59 (0.22%) |
| September 2023 | 26,630 | 36 (0.14%) |



HA will continue monitoring the use of Rosuvastatin in Hong Kong

Thank 