

Interaction between **rosuvastatin** and **ticagrelor** resulting in **rhabdomyolysis**

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Background

A signal screening focusing on drug-drug interactions in VigiBase, the WHO global database of individual case safety reports, identified a case series pointing to an interaction between the platelet aggregation inhibitor ticagrelor and the statin rosuvastatin leading to rhabdomyolysis. Rhabdomyolysis is a well-known adverse drug reaction of statins. The risk of developing rhabdomyolysis is concentration dependent and is increased in elderly patients and in patients with renal and/or hepatic impairment[1].

Aim

To explore a possible interaction between rosuvastatin and ticagrelor leading to rhabdomyolysis.

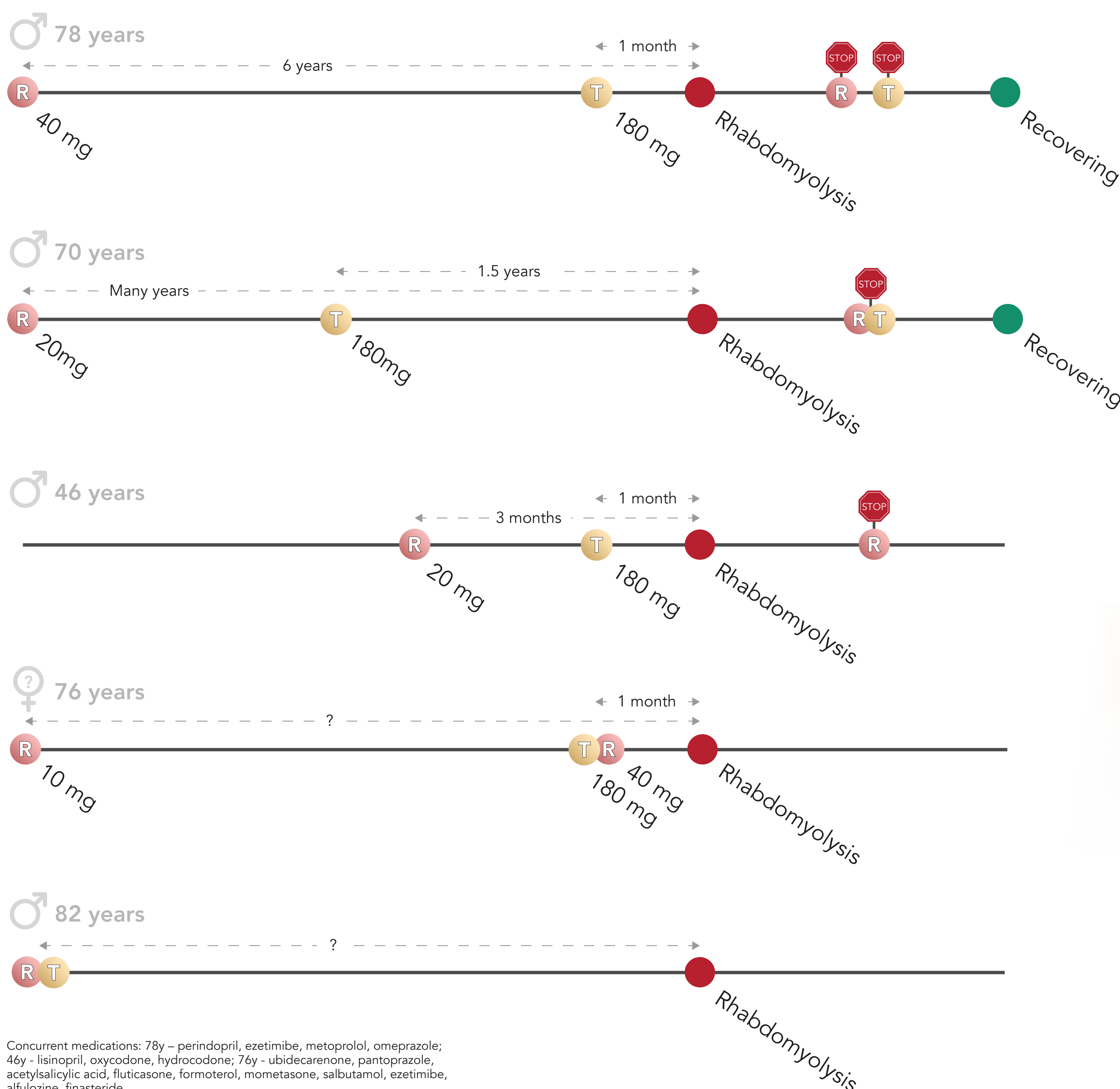
Methods

Clinical review of reports with rhabdomyolysis and concurrent use of rosuvastatin and ticagrelor, included in VigiBase up to October 2016.

Results

VigiBase contained five unique cases reporting rhabdomyolysis with ticagrelor and rosuvastatin as suspected medications. The reports originated from five countries in North America and Europe (including one literature case[2]). Patient ages, daily doses of rosuvastatin and the time relationship between rhabdomyolysis and exposure of rosuvastatin and ticagrelor are presented in the time lines below. In two cases the patient had used rosuvastatin for years without complaints before ticagrelor was added. Two cases reported concurrent use of ezetimibe, which increases the AUC of rosuvastatin 1.2 times[1]. Two cases reported concurrent use of ACE-inhibitors, which can cause renal dysfunction[3]. After discontinuation of both ticagrelor and rosuvastatin in two cases, the symptoms regressed or disappeared.

R Rosuvastatin **T** Ticagrelor

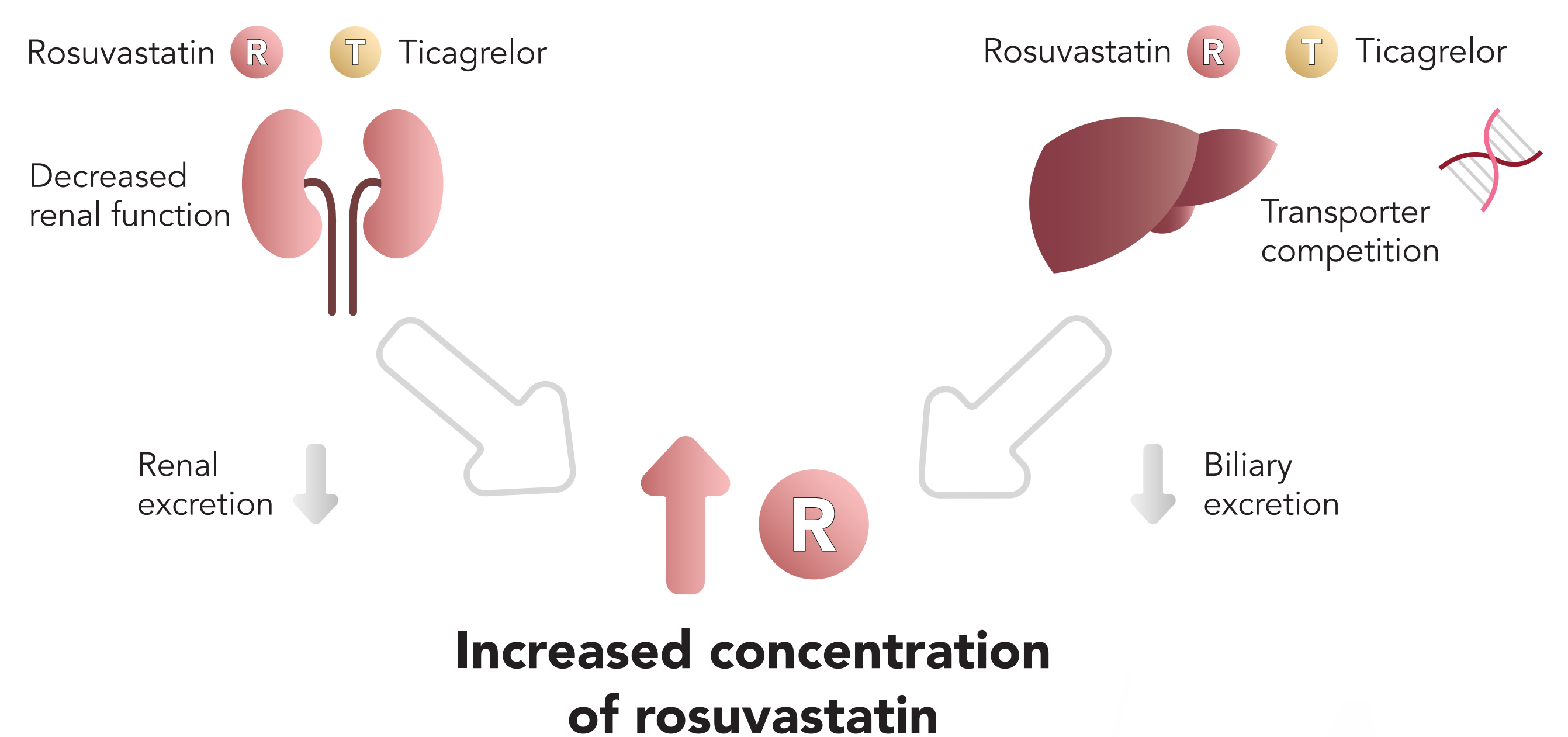


Conclusions

The reports in VigiBase presented one or more risk factors for rhabdomyolysis: old age, higher than recommended rosuvastatin dose, and/or concurrent use of drugs that may affect rosuvastatin concentration. In these cases, the start of ticagrelor seems to have added an additional risk, raising rosuvastatin concentration to critical levels, resulting in rhabdomyolysis. This is supported by a plausible temporal association in three cases.

Rosuvastatin is mainly eliminated by biliary excretion, and to a lesser extent by renal excretion[1]. An interaction with ticagrelor possibly includes mechanisms affecting both elimination pathways:

- Renal impairment caused by ticagrelor, leading to decreased renal excretion of rosuvastatin
- Competition on transporter level (OATP1B1), leading to decreased biliary excretion of rosuvastatin
- Genetic polymorphism (OATP1B1 and/or UGT2B7), leading to increased competition on transporter level [1,4,5]



In conclusion, the reports in VigiBase, together with plausible mechanisms, support a signal for an interaction between ticagrelor and rosuvastatin especially in high-risk patients.

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Disclosure

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