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Ticagrelor and rosuvastatin interaction leading to rhabdomyolysis and acute renal failure

Interakcja tikagreloru i rozuwastatyny prowadząca do rabdomiolizy i ostrej niewydolności nerek

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Abstract

Dual antiplatelet therapy with acetylsalicylic acid and oral inhibitors of the P2Y12 receptor is the cornerstone of acute coronary syndrome management. It is recommended to use a combination of acetylsalicylic acid and ticagrelor, regardless of the initial therapy. Ticagrelor is unique among inhibitors of the platelet P2Y12 receptor because it does not require metabolic activation, it binds to the receptor in a reversible manner and through, inter alia, increasing the concentration of adenosine has a wide pleiotropic effect. But interactions between ticagrelor and statins may also lead to myopathy and rhabdomyolysis. This is because ticagrelor metabolized by the cytochrome CYP3A4 is a competing substrate, it delays the metabolism potentiating the effects of statins also metabolized by CYP3A4. Although rosuvastatin is metabolized by a different cytochrome, that is CYP2C9 and ticagrelor is a CYP3A4 substrate, over a dozen of rhabdomyolysis resulting from their interaction have been reported. The article discusses the case of a 77-year-old woman admitted to the geriatric department 3 weeks after non-ST segment elevation acute coronary syndrome, after percutaneous angioplasty with DES stent implantation. The patient was burdened with type 2 diabetes, hypertension, dyslipidemia, hyperuricemia, chronic kidney disease, heart failure with reduced EF, obesity and asthma. She was discharged from the cardiology department with the recommendation to use inter alia ticagrelor at the dose of 180 mg/day, aspirin 75 mg/day and rosuvastatin 40 mg/day. Based on the reported symptoms, such as severe weakness, difficulty walking, significantly less urination and laboratory tests results: creatine kinase 44167 U/l, creatinine 240.6 μmol/l (GFR 17.99 ml/min/1.73 m^2), urea 14.56 mmol/l and ALT 231 U/l, AST 781 U/l, a diagnosis of rhabdomyolysis caused by interaction of ticagrelor with rosuvastatin was made. On the second day of hospitalization, rosuvastatin and ticagrelor were discontinued. Because the renal parameters worsened (creatinine 474.0 μmol/l, GFR 8.23 ml/min/1.73 m^2, urea 28.10 mmol/l), on the fourth day the first, and total of five hemodialysis treatments were performed during the entire hospitalization.. The patient was discharged from the geriatric ward after 3 weeks of hospitalization in good condition, with good diuresis, with normal values of CK, ALT, AST, urea and still yet elevated creatinine 235.0 μmol/l (GFR 18.49 ml/min/1.73 m^2). (Gerontol Pol 2022; 30; 188-193) doi: 10.53139/GP.20223024

Keywords: *acute renal failure, rhabdomyolysis, rosuvastatin, ticagrelor*

Streszczenie

Podwójna terapia przeciwpłytkowa kwasem acetylosalicylowym i doustnymi inhibitorami receptora P2Y12 jest podstawą postępowania w ostrym zespole wieńcowym. Zalecane jest połączenie kwasu acetylosalicylowego i tikagreloru, niezależnie od leczenia początkowego. Tikagrelor różni się od innych inhibitorów płytkowego receptora P2Y12, ponieważ nie wymaga aktywacji metabolicznej, wiąże się z receptorem w sposób odwracalny i poprzez miedzy innymi zwiększenie stężenia adenozyny wykazuje szerokie działanie plejotropowe. Interakcje między tikagrelorem a statynami mogą jednak prowadzić niekiedy do miopatii i rabdomiolizy. Dzieje się tak, ponieważ tikagrelor metabolizowany też przez cytochrom CYP3A4 jest substratem konkurującym, opóźnia metabolizm, nasilając działanie statyn metabolizowanych przez CYP3A4 i chociaż rosuwastatyna jest metabolizowana przez cytochrom CYP2C9, a tikagrelor jest substratem dla CYP3A4, opisano dotychczas kilkanaście przypadków rabdomiolizy wynikających z ich interakcji. W artykule omówiono przypadek 77-letniej kobiety, która została przyjęta do oddziału geriatrii 3 tygodnie po ostrym zespole wieńcowym bez uniesienia odcinka ST, po zabiegu przezskórnej angioplastyki z implantacją stentu DES. Pacjentka obciążona wielochorobowo-

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ścią: cukrzyca typu 2, nadciśnienie tętnicze, dyslipidemia, hiperurykemia, przewlekła choroba nerek, niewydolność serca z obniżoną frakcją wyrzutową, otyłość i astma. Została wypisana z oddziału kardiologii z zaleceniem stosowania miedzy innymi tikagreloru w dawce 180 mg/d, aspiryny 75 mg/d i rosuwastatyny 40 mg/d. Na podstawie występujących objawów, takich jak silne osłabienie, trudności w chodzeniu, znacznie zmniejszenie ilości oddawanego moczu oraz wyników badań laboratoryjnych: kinaza kreatynowa 44167 U/l, kreatynina 240,6 μmol/l (GFR 17,99 ml/min/1,73 m^2), mocznik 14,56 mmol/l, ALT 231 U/l, AST 781 U/l, postawiono rozpoznanie rabdomiolizy wywołanej interakcją tikagreloru z rosuwastatyną. W drugiej dobie hospitalizacji odstawiono rozuwastatynę i tikagrelor. Ze względu na pogorszanie się parametrów nerkowych: kreatynina 474,0 μmol/l, GFR 8,23 ml/min/1,73 m^2, mocznik 28,10 mmol/l w czwartej dobie wykonano pierwszy, i łącznie podczas całego pobytu pięć zabiegów hemodializy. Pacjentka została wypisana z oddziału geriatrii po 3 tygodniach w stanie ogólnym dobrym, z prawidłową diurezą i wynikami badań: CK, ALT, AST, mocznika, z utrzymującym się jeszcze podwyższonym poziomem kreatyniny 235,0 μmol/l (GFR 18,49 ml/min/1,73 m^2). (Gerontol Pol 2022; 30; 177-193) doi: 10.53139/GP.20223024

Słowa kluczowe: *ostra niewydolność nerek, rabdomioliza, rozuwastatyna, tikagrelor*

Introduction

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and oral inhibitors of the P2Y12 receptor for adenosine 5'-diphosphate (ADP) is the cornerstone of acute coronary syndrome management. According to the guidelines of the European Society of Cardiology (ESC) it is recommended for 12 months in the case of myocardial infarction with persistent ST segment elevation and in non-ST segment elevation acute coronary syndrome (NSTE-ACS), regardless of the type of treatment used (conservative management vs. revascularization). and the type of stent being implanted. Treatment may be shortened to a month (conservative management) or 6 months (revascularization with stent implantation) and extended to more than 12 months based on the individual patient's risk of bleeding or ischemic. In patients with stable coronary artery disease (SCAD) undergoing percutaneous coronary intervention (PCI), the recommended duration of DAPT is 6 months. A reduction to 3 months or an extension of DAPT beyond 12 months may be considered taking into account the individual bleeding risk.

The recommended medications for ACS is a combination of ASA with ticagrelor, regardless of the initial therapy. The combination of ASA and clopidogrel is the preferred combination in patients with ACS treated conservatively, with a high risk of bleeding and with SCAD undergoing PCI [1,2].

According to current guidelines of ESC and EAS (European Atherosclerosis Society) the goal in the treatment of dyslipidemia in patients after myocardial infarction is reduce the initial LDL-cholesterol by at least 50% to levels below 55 mg/dl. In acute myocardial infarction, the highest possible dose of a statin should be administered, regardless of the LDL-cholesterol level, and similar loading doses of a statin should be given before coronary angioplasty [3].

Despite the benefits of antiplatelet and lipid-lowering treatments, interactions between ticagrelor and statins may lead also into myopathy and rhabdomyolysis. This is because ticagrelor metabolized by the cytochrome CYP3A4, acts as a competing substrate, delays the metabolism potentiating the effects of statins also metabolized by CYP3A4. An exception may be rosuvastatin, which independent of CYP3A4 metabolism.

Nevertheless, a dozen or so cases of rhabdomyolysis caused by the interaction of ticagrelor and rosuvastatin have been described [4-12].

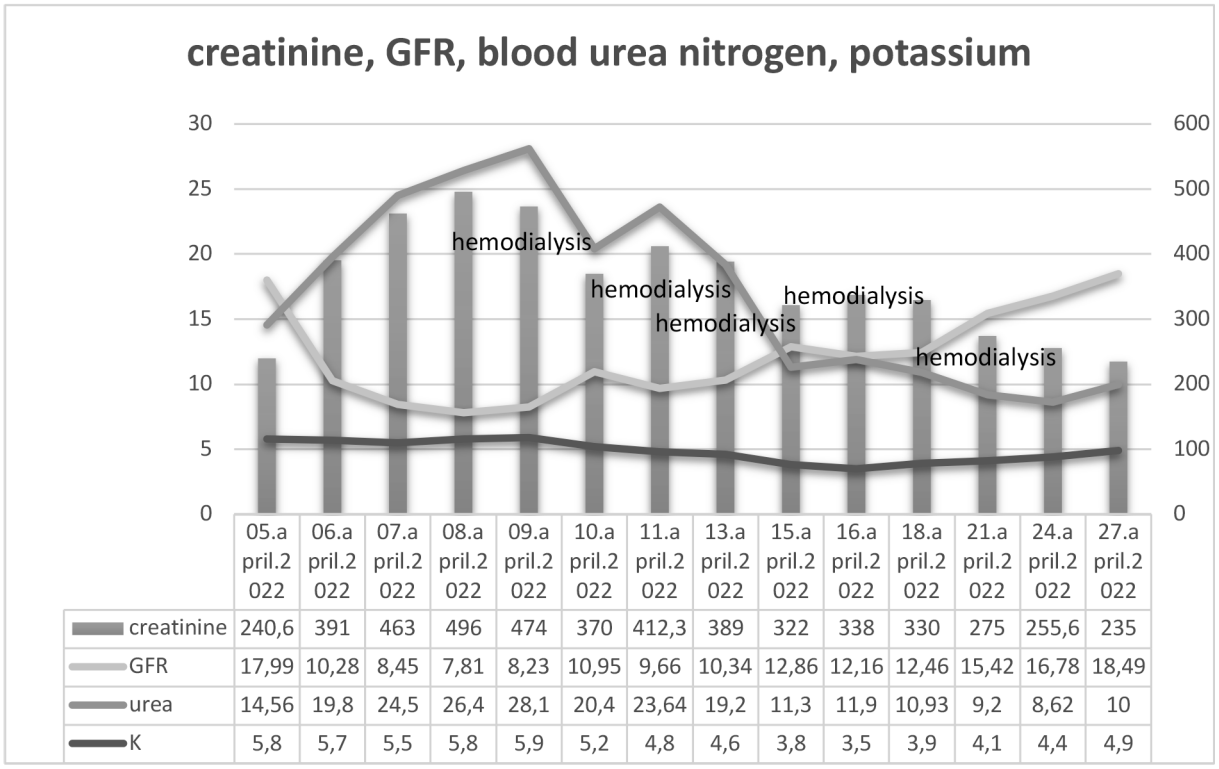
Case Presentation

A 77-year-old women was admitted to the geriatric department as a matter of urgency due to severe weakness, difficulties with walking and much less urination. She noted also, that urine was turned a dark brown color. Two weeks earlier, she was discharged from the cardiology department, where due to non-ST segment elevation acute coronary syndrome, she underwent percutaneous angioplasty with DES stent implantation to the critical stenosis of LCx (left circumflex artery). The patient burdened with multimorbidity: type 2 diabetes treated with metformin (HbA1c 12.30 %), grade I hypertension ESC/ESH (144/98 mmHg), dyslipidemia (cholesterol 4.97 mmol/l, LDL-cholesterol 2.52 mmol/l, HDL-cholesterol 1.19 mmol/l, tryglicerides 2.75 mmol/l), hyperuricemia (uric acid 349 umol/l), chronic kidney disease, stage G3a (GFR 53,2 ml/min/1.73 m^2), obesity BMI 32.4 kg/m^2, heart failure with reduced EF (EF ~40%) and well-controlled asthma.

The creatinine level increased after coronary angioplasty from 53.23 μmol/l to 143.5 μmol/l (n = 44.0-80.0), GFR decreased from >90 ml/min/1.73 m^2 to 32.66 ml/min /1.73 m^2. The high baseline aspartate and alanine aminotransferase: ALT 69 U/l (n: 0-33) and AST 258 U/l (n: 0-32) values were not controlled during her stay at the

cardiology department. After 8 days she was discharged from the cardiology department with the recommendation to use ticagrelor at the dose of 180 mg/day, aspirin 75 mg/day, bisoprolol 10 mg/day, ramipril 2.5 mg/day, rosuvastatin 40 mg/day and short-acting insulin aspart 3 times a day with meals and basal NPH insulin at nigh with daily blood glucose monitoring. In addition, she was also to take a proton pump inhibitor at the dose 20 mg/day (pantoprazole).

On admission to the geriatric ward, she was lying down, unable to sit up on her own and assume a standing position. The arterial pressure was 162/84 mmHg and the heart rate was 75/min. The heart sounds were quiet. Over the lung fields were present vesicular breath



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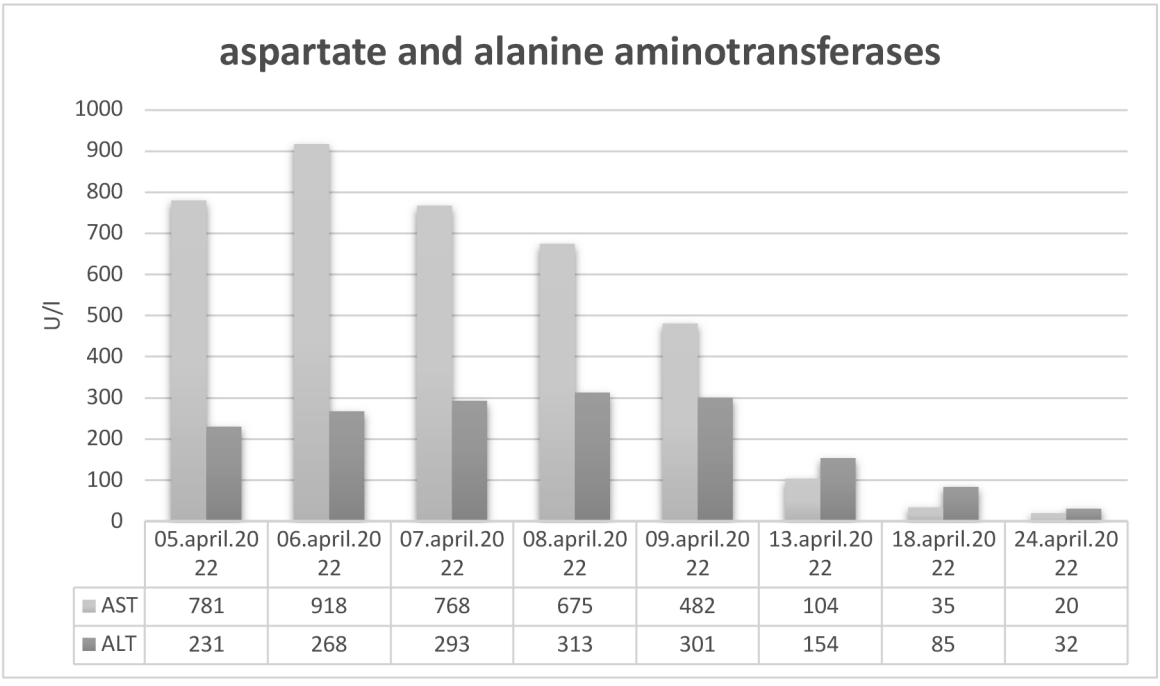
creatinine	240,6	391	463	496	474	370	412,3	389	322	338	330	275	255,6	235
GFR	17,99	10,28	8,45	7,81	8,23	10,95	9,66	10,34	12,86	12,16	12,46	15,42	16,78	18,49
urea	14,56	19,8	24,5	26,4	28,1	20,4	23,64	19,2	11,3	11,9	10,93	9,2	8,62	10
K	5,8	5,7	5,5	5,8	5,9	5,2	4,8	4,6	3,8	3,5	3,9	4,1	4,4	4,9

Figure 1. Creatinine, GFR, urea and potassium levels during hospitalization



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AST	781	918	768	675	482	104	35	20
ALT	231	268	293	313	301	154	85	32

Figure 2. AST and ALT levels during hospitalization

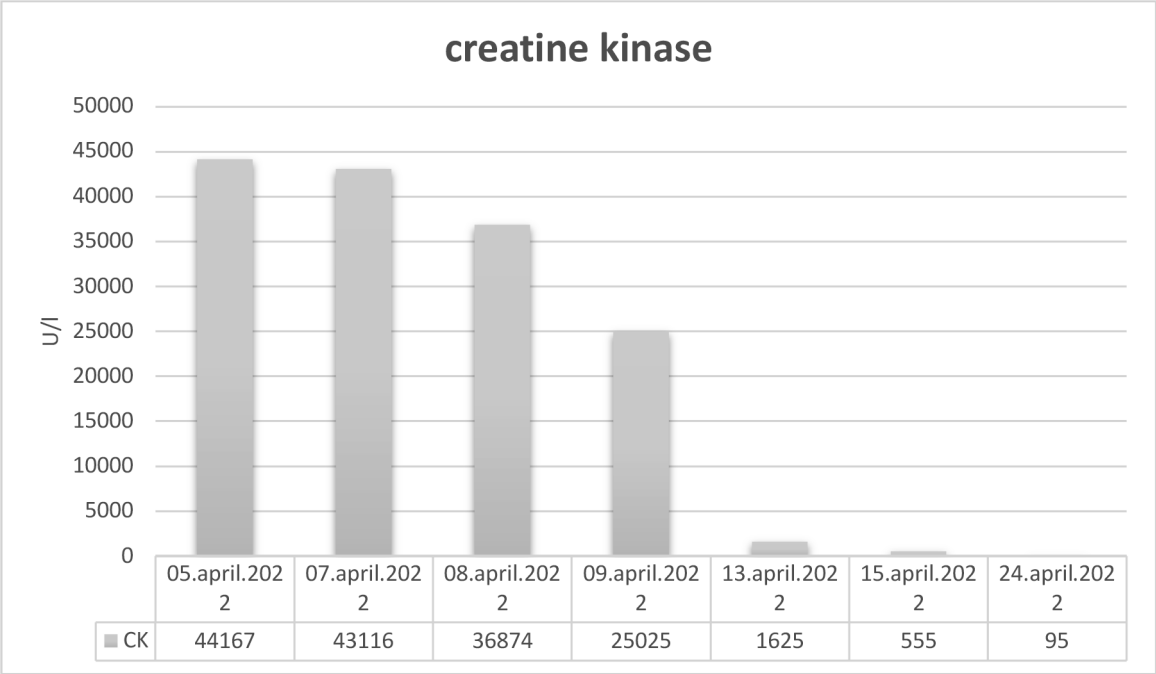

Figure 3. Creatine kinase level during hospitalization

sounds. There was slight swelling on the calves and feet. Laboratory tests performed on the day of admission revealed very high creatinine values of 240.6 μmol/l (GFR 17.99 ml/min/1.73 m²), urea 14.56 mmol/l (n = 2.76-8.07), ALT 231 U/l, AST 781 U/l and creatine kinase (CK) 44167 U/l (n = 0-170). Suspecting rhabdomyolysis, rosuvastatin and ticagrelor were discontinued on the second day of hospitalization. Ticagrelor has been replaced with clopidogrel. Rehydration solution and intensive insulin therapy were carried out. The patient's condition was good, diuresis was normal, and blood pressure was 140/90 mmHg. The level of CK 25025 U/l, ALT 301 U/l and AST 482 U/l decreased. However, the renal parameters deteriorated: creatinine 474.0 μmol/l, GFR 8.23 ml/min, urea 28.10 mmol/l. On the fourth day after insertion of the dialysis time catheter, the first hemodialysis treatment was performed. A total of five hemodialysis treatments were performed. 2-unit of red blood cells were also transfused. The patient was discharged from the geriatric ward after three weeks of hospitalisation in good condition, with good diuresis, with normal values of CK 95 U/l, ALT 32 U/l, AST 20 U/l, urea 10.00 mmol/l. The creatinine level was at the level of 235.0 μmol/l, GFR 18.49 ml/min/1.73 m² (figure 1-3).

Discussion

Ticagrelor, unlike other antiplatelet drugs, blocks the platelet P2Y12 receptor in a reversible way, does not require metabolic activation, by increasing the concentration of adenosine it has a pleiotropic/anti-inflammatory effect (cardioprotection, restoration of the myocardium after an ischemic event, promotion of the release of anticoagulative factors) and importantly, is metabolized independently of the interindividual genetic variability [13]. The PLATO (*Platelet Inhibition and Patient Outcomes*) trial demonstrated lower mortality rates with the use of ticagrelor when compared to clopidogrel (9.8% vs 11.7%, p<0.001) when treating patients with acute coronary syndrome. Additionally, when investigating a potential ticagrelor-statin interplay, it was found that co-administration of ticagrelor and statins decrease both vascular and all-cause mortality, compared to clopidogrel and statins. This may be because ticagrelor, unlike clopidogrel, significantly increases the potency of statins metabolized by CYP3A4, which in turn may increase the vascular benefit of their [14]. On the other side, an increased risk of rhabdomyolysis has also been shown when ticagrelor is administered together with high-dose statins, especially in patients with chronic kidney disease CKD [13,15].

The risk of rhabdomyolysis and myoglobinuria-induced acute tubular necrosis in patients treated with statins is increased because ticagrelor, a enzymatic inhibitor for CYP3A4 (and CYP3A5), witch delay metabolism and leading to statins accumulation. The second mechanism that increases statin retention may be ticagrelor-induced renal insufficiency [15].

In contrast to simvastatin, lovastatin and atorvastatin, which are metabolized by CYP3A4, rosuvastatin is metabolized only in minor extend (approximately 10%),

the majority of the drug is excreted in the unchanged form. The most potent isoenzyme involved in rosuvastatin (but also fluvastatin and pitavastatin) metabolism is CYP2C9, to a lesser extent others (1A2, 2C19, 2D6, 2E1, and 3A4). The role of other mechanisms involved in statin metabolism, e.g. organic anion transporter polypeptides (OATP) and P-glycoprotein, is unclear. However, it is known that SLCO1B1 gene polymorphisms may reduce activity of OATP1B1 that affects the hepatic uptake of especially hydrophilic statins (pitavastatin, pravastatin and rosuvastatin), thereby reducing their efficacy and increasing plasma concentrations, what consequently is associated with an increased risk of muscle toxicity [16,17]. On the other hand it is known that the age of the patient itself may be the strongest risk factor for statin-associated muscle symptoms [18].

In the PLATO trial, serum creatinine concentration increased by more than 30% in more than 25.5% of the patients receiving ticagrelor. The worsening renal function may be more pronounced in older patients over 75 years of age, receiving angiotensin receptor inhibitors, and with pre-existing renal dysfunction [19,20]. The mechanism explaining the worsening of renal function with the use of ticagrelor is probably inhibition of adenosine reuptake what reduces the glomerular filtration rate of the afferent renal arteriole [21].

Although ticagrelor may worsen renal function, no its dose adjustment is necessary in patients with their impairment. However, the dose of statin should be reduced. As recommended EMA (European Medicines Agency), rosuvastatin is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment (creatinine clearance < 60 ml/min). The recommended start dose in this case is 5 mg [22].

Generally, the incidence of statin-associated rhabdomyolysis is approximately 1 case/10,000 person-years. It is diagnosed based by increases level of CK >10× ULN (upper limit of normal), without other causes of muscle injury and presence of evidence of renal compromise [23]. Up to 50% of patients suffering from rhabdomyolysis develop acute kidney injury (AKI) and can damage the liver. The main effect of haemoproteins on the kidneys is their direct tubule cell toxicity (necrosis and apoptosis, pyro- and ferroptosis). Hemodialysis is often the treatment of choise for severe rhabdomyolysis [23,24].

Conclusion

The risk of an interaction between rosuvastatin and ticagrelor leading to rhabdomyolysis and acute renal failure should be always taken into account in elderly patients, especially these with pre-existing renal failure and receiving angiotensin receptor inhibitors, despite the lack of interaction in their metabolism.

Conflict of interest
none

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