

# Approaches to management of rhabdomyolysis as the adverse effect of drug interaction between atorvastatin and sacubitril/valsartan: a case report

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Received 23 July 2021; first decision 6 September 2021; accepted 18 February 2022; online publish-ahead-of-print 22 February 2022

## Background

Atorvastatin and sacubitril/valsartan (Entresto<sup>TM</sup>) have been cornerstones in managing patients with coronary artery disease and heart failure (HF). We report a case of life-threatening rhabdomyolysis associated with the co-administration of atorvastatin and sacubitril/valsartan.

## Case summary

A 58-year-old male with coronary heart disease and chronic HF treated with the optimal dose of atorvastatin and other cardiovascular medications was frequently admitted for acute decompensation of HF. We decided to optimize his condition by adding sacubitril/valsartan to his treatment regime. He presented to our outpatient clinic with worsening myalgia and oliguria 6 days later. He was readmitted with markedly elevated serum creatinine kinase (CK) (94 850 U/L; normal range 32–294 U/L), deranged liver function tests, and acute kidney injury. We withheld atorvastatin and sacubitril/valsartan and treated him with renal replacement therapy.

## Discussion

Sacubitril inhibits the excretion of statins, thereby elevating serum statin concentration and increasing the likelihood of developing muscle-related toxicity. Co-administration of atorvastatin and sacubitril/valsartan should be monitored closely with laboratory investigations of CK and liver and renal function. The physician may consider starting low-dose atorvastatin at 20 mg daily in combination with sacubitril/valsartan 24 mg/26 mg twice daily and titrating accordingly to optimal doses. Rosuvastatin could be an alternative to atorvastatin, as it has less drug–drug interaction with sacubitril, thereby reducing the adverse effect.

## Keywords

Atorvastatin • Sacubitril/valsartan (Entresto<sup>TM</sup>) • Drug interaction • Rhabdomyolysis • Case report

## ESC Curriculum

3.1 Coronary artery disease • 6.2 Heart failure with reduced ejection fraction • 7.3 Critically ill cardiac patient

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Handling Editor: Daniel Bromage

Peer-reviewers: Edgar Francisco Carrizales; Ching-Hui Sia

Compliance Editor: Zhiyu Liu

Supplementary Material Editor: Katharine Kott

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## Learning points

- An elevation in serum creatinine kinase and deranged liver function tests in patients who are treated with statins and sacubitril should prompt the physician to consider statin-related muscle toxicity.
- Co-administration of low dose of atorvastatin 20 mg daily in combination with sacubitril/valsartan 24 mg/26 mg twice daily and titrate according to the recommended optimal doses provided that there is no evidence of muscle-related toxicity.
- There may be a potential role of rosuvastatin as the alternative for atorvastatin in combination with sacubitril/valsartan that may associated with a lower rate of drug interactions.

## Introduction

Coronary artery disease (CAD) is the leading cause of heart failure (HF). To date, treatments revolve around the management of conventional cardiovascular risk factors and the complications of HF. The use of high-intensity statins, such as atorvastatin and rosuvastatin, has been recommended for the secondary prevention of major adverse cardiovascular events (MACE).<sup>1</sup> The side effects of statins include myalgia, transaminitis and, rarely, rhabdomyolysis.<sup>2</sup> Meanwhile, the sacubitril/valsartan combination therapy has been increasingly used among the HF population as a superior alternative to angiotensin-converting enzyme inhibitors in terms of reducing the risk of cardiovascular death and hospitalization for HF. Its known adverse effects are hypotension, hyperkalaemia, acute kidney injury, and very rarely angio-oedema, but it was not known to cause rhabdomyolysis.<sup>3</sup>

Rhabdomyolysis is a clinical syndrome characterized by muscle cell damage, leading to raised serum creatinine kinase (CK) and deranged liver enzymes, which results in clinical sequelae that include life-threatening electrolyte disturbances, cardiac arrhythmias, and acute kidney injury. Clinical manifestations include myalgia, muscle weakness, and myoglobinuria, which presents as tea-coloured urine.<sup>4</sup> We describe a case of life-threatening rhabdomyolysis secondary to a drug interaction between atorvastatin and sacubitril/valsartan. This case emphasizes the importance of monitoring for adverse effects after commencement of a medication and management approaches to reduce adverse events secondary to drug interactions.

## Timeline

Date	Events
2018	Admitted for acute coronary syndrome, was treated with percutaneous coronary intervention and optimal medical therapy.
2019–2020	Patient was recurrently admitted for acute decompensation of heart failure (HF).
7 January 2021	Admitted for acute decompensation of HF and perindopril was withheld 2 days prior discharge. He was then discharged home with sacubitril/valsartan.

*Continued*

### Continued

Date	Events
13 January 2021 (Day 1)	Presented to clinic with rhabdomyolysis and acute kidney injury as evident by markedly elevated serum creatinine, creatinine kinase (CK), and deranged liver function test. He was admitted on the same day.
14 January 2021 (Day 2)	Atorvastatin and Sacubitril/Valsartan were withheld. He was started with intravenous rehydration therapy with furosemide guided by central venous pressure.
15 January 2021 (Day 3)	Nephrology team was consulted inpatient for renal replacement therapy in view of worsening creatinine and developed anuria. Sustained low efficiency dialysis (SLED) was commenced on the same day.
16 January 2021 (Day 4)	Developed cardiogenic shock secondary to acute coronary syndrome with raised troponin I post-SLED. He was started with noradrenaline inotropic support.
20 January 2021 (Day 8)	Weaned down from inotropic support.
22 January 2021 (Day 10)	Improved renal function, liver function, and serum CK.
24 January 2021 (Day 12)	Discharged home with rosuvastatin in view of persistently elevated serum low-density lipoprotein.
1 February 2021	Decision to restart low-dose sacubitril/valsartan in view of normalized renal and liver function test.
15 February 2021	He tolerated both low-dose rosuvastatin and sacubitril/valsartan.

## Case presentation

A 58-year-old male with underlying ischaemic heart disease, heart failure (HF), dyslipidaemia, and Stage 3 chronic kidney disease presented to the clinic for follow-up. He was admitted 2 years prior for myocardial infarction and managed appropriately with percutaneous coronary intervention, followed by optimal medical therapy. His

baseline left ventricular ejection fraction was 20%. Since diagnosis, he has been treated with the following medications: atorvastatin 80 mg daily, aspirin 100 mg daily, perindopril 4 mg daily, bisoprolol 5 mg daily, furosemide 40 mg twice daily, and spironolactone 25 mg daily. Despite compliance with his treatment, he has had five admissions for acute decompensation of HF over the past 2 years. We withheld the perindopril from his medication list 2 days prior to discharge. His baseline serum potassium level was 4 mmol/L, which is within the normal range; he also had normal hepatic function and no electrolyte abnormalities. Subsequently, we optimized his HF treatment with the addition of sacubitril/valsartan 49 mg/51 mg twice daily upon discharge.

Six days after discharge, he presented with progressively worsening myalgia, oliguria, generalized malaise, and lethargy. Upon admission, his blood pressure was 96/60 mmHg (mean arterial pressure 70 mmHg), heart rate 90 b.p.m., and his pulse oximetry was 97% under room air. Physical examination revealed bibasal crepitation on auscultation of the lung and bilateral lower limb oedema. Baseline laboratory investigation upon admission was significant for elevated serum creatinine (680  $\mu\text{mol/L}$ ; baseline 153  $\mu\text{mol/L}$ ), alanine aminotransferase (ALT) of 351 U/L (normal range 10–49 U/L), aspartate aminotransferase (AST) of 1499 U/L (normal range < 34 U/L), and markedly raised CK of 94 850 U/L (normal range 32–294 U/L). Other relevant investigations, such as high-sensitivity troponin I, serum potassium, electrolytes, full blood count, and coagulation profile, were unremarkable. A bedside transthoracic echocardiogram revealed dilated right and left atria, with a reduced left ventricular ejection fraction of 15–20%.

A provisional diagnosis of acute kidney failure secondary to rhabdomyolysis aggravated by sacubitril/valsartan was made. The

cardiologist decided to withhold his atorvastatin and sacubitril/valsartan because of possible drug interactions. Intravenous rehydration therapy was initiated together with IV furosemide 40 mg twice daily. The amount of fluid infused daily was carefully guided by central venous pressure, which we aimed to maintain between 8 and 10 cmH<sub>2</sub>O. On Day 3 of admission, he developed anuria with worsening serum creatinine (931  $\mu\text{mol/L}$ ) and was referred to the nephrology team for urgent renal replacement therapy. The nephrology team commenced sustained low efficiency dialysis (SLED) and he developed hypotension and chest discomfort post-SLED. The post-SLED blood investigation showed improved serum creatinine of 584  $\mu\text{mol/L}$ , CK of 40 956 U/L with repeated high-sensitivity troponin I of 3.89 ng/mL (normal range < 0.06 ng/mL). A provisional diagnosis of cardiogenic shock secondary to acute coronary syndrome was established. Coronary angiogram was not performed due to the increased risk of contrast-induced nephropathy. We commenced noradrenaline inotropic support and treated him with aspirin, ticagrelor, and fondaparinux in the cardiac intensive care unit. He required noradrenaline inotropic support for the next 4 days and dobutamine inotropic support briefly, which were subsequently tapered off.

On the 10th day of admission, his condition stabilized with markedly reduced serum creatinine, CK, ALT and AST. The patient was restarted on low-dose rosuvastatin 5 mg daily upon discharge because of persistently elevated serum low-density lipoprotein (LDL) of 4.1 mmol/L. An outpatient clinic follow-up 1 week later revealed normalized renal and liver function; hence, the decision to restart low-dose sacubitril/valsartan 24 mg/26 mg was made. He tolerated the co-administration of both low-dose rosuvastatin and sacubitril/valsartan as evidenced by static renal and liver profiles on the subsequent clinic visit (Table 1).

**Table 1** Laboratory investigation

Investigation/day of admission	Reference range	7 days prior	Day 1	Day 3	Day 4 (post-SLED)	Day 10	Day 12	Clinic 1	Clinic 2
Renal function test									
Urea (mmol/L)	3–8	8	19	36.1	20.1	10.1	9.8	9.5	9.7
Creatinine ( $\mu\text{mol/L}$ )	54–97	153	680	931	584	160	159	159	160
Potassium (mmol/L)	3.5–5.2	4	4.1	4.9	3.2	3.5	3.7	4.1	4.2
eGFR (mL/min/1.72 m <sup>2</sup> )	>90	46	10	8	12	44	44	44	44
Liver function test									
ALT (U/L)	10–49	38	351	309	250	58	55	53	50
AST (U/L)	<34	27	1499	1140	980	101	98	50	45
Others									
Creatinine kinase (U/L)	32–294	52	94 850	63 350	40 956	2739	1180	420	317
Corrected calcium (mmol/L)	2.2–2.6	2.1	2.02	2.0	2.1	2.2	2.2		
Magnesium (mmol/L)	0.5–1.1	0.92	1.2	1.2	0.9	1.0	1.1		
Phosphate (mmol/L)	0.78–1.65	2.1	2.8	3.2	1.9	2.0	2.08		
Troponin I (ng/mL)	<0.06		0.1		3.89				
LDL (mmol/L)	<2.6	4.2				4.1			4.0
Full blood count		Normal	Normal		Normal	Normal			
Coagulation profile		Normal	Normal		Normal	Normal			
Left ventricular ejection fraction (LVEF, %)		20	15				15		15

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.

## Discussion

Dyslipidaemia is a known cardiovascular risk factor for CAD. The use of statins has been well established as a secondary preventive strategy to reduce cardiovascular events and mortality.<sup>5</sup> In recent years, studies have concluded that high-intensity statins are superior for lowering the risk of MACE; therefore, CAD patients have been treated with atorvastatin or rosuvastatin.<sup>1,6</sup> Our patient had received an optimal dose of atorvastatin and his CK and liver function test remained normal throughout the 2 years of follow-up. However, he had multiple admissions for acute decompensation of HF. For this reason, sacubitril/valsartan was added to reduce his risk of hospitalization and death from HF.<sup>3</sup> The addition of sacubitril/valsartan seemed to contribute to the development of rhabdomyolysis associated with the alteration of atorvastatin metabolism by sacubitril/valsartan. The known risk factors for statin-associated muscle symptoms include increased age, female gender, renal disease, diabetes mellitus, and drug interactions that affect statin pharmacokinetics.<sup>7</sup> Our patient had several risk factors, namely advanced age, renal disease, and drug interactions that predisposed him to statin-associated muscle symptoms. Several case reports have described similar risk factors and the presentation of rhabdomyolysis soon after the addition of sacubitril/valsartan.<sup>8–10</sup> Rawla et al.<sup>11</sup> had recorded a case with similar underlying risk factors for rhabdomyolysis reported sacubitril/valsartan as the only drug that could account for rhabdomyolysis (Table 2).

The postulated mechanism for statin-induced rhabdomyolysis is the drug–drug interaction that results in elevated maximum serum statin concentration ( $C_{max}$ ), accounting for muscle-related toxicity

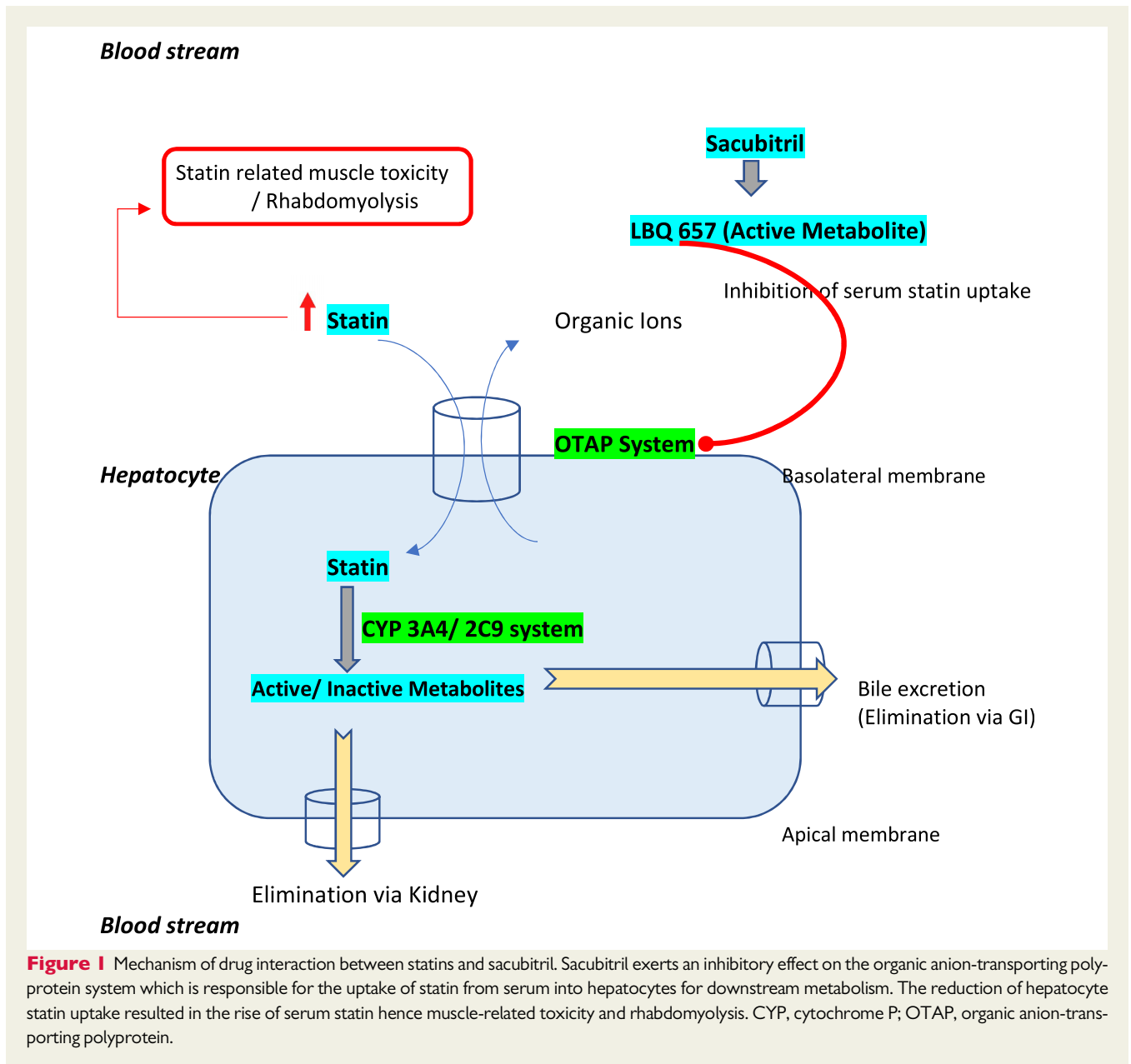
and severe rhabdomyolysis.<sup>12</sup> The organic anion transporting polypeptide (OATP) system enables the uptake of statins into hepatocytes, whereas hepatic cytochrome P450 is involved in the metabolism of statins for renal and bile excretion.<sup>13</sup> Cytochrome P inhibitors restrain the enzyme activity of cytochrome P2C9 and cytochrome P3A4, thus reducing statin metabolism and subsequently increasing plasma  $C_{max}$ .<sup>14</sup> Medications, such as fibrates, calcium channel blockers, antifungals and antiretrovirals, are cytochrome P450 inhibitors that commonly interact with atorvastatin.<sup>14</sup> Sacubitril/valsartan is not known to inhibit cytochrome P450 activity. The postulated mechanism of drug interaction between atorvastatin and sacubitril/valsartan is the inhibition of the OATP family. Sacubitril, a prodrug that inhibits OATP1 B1 activity, leads to a reduction in rate-limiting atorvastatin and the bile or renal elimination of its metabolites<sup>12,13,15</sup> (Figure 1). The evidence suggests that the co-administration of atorvastatin and sacubitril increases the likelihood of statin-induced rhabdomyolysis, as both drugs reach  $C_{max}$  at a similar time, and sacubitril exerts a maximal inhibitory effect on the elimination of atorvastatin<sup>15</sup> (Table 3).

Concurrent treatment with sacubitril/valsartan and high-intensity statins has the potential to significantly reduce cardiovascular morbidity and all-cause mortality among populations with HF and dyslipidaemia. Statins have been proven to reduce MACE and all-cause mortality, with a number needed to treat (NNT) of 72 and 250, respectively. The suggested approach to monitor on adverse effects would be muscle-related symptoms followed by liver function and serum creatinine after commencement of statin therapy.<sup>16,17</sup> Meanwhile, sacubitril/valsartan has demonstrated estimated NNT

**Table 2** Literature review of cases on statins or sacubitril/valsartan associated rhabdomyolysis<sup>8–11</sup>

Case	Our patient	Previsdomini et al.	Faber et al.	Chan et al.	Rawla et al.
Age/gender/premorbid	58/male/DM, dyslipidaemia, CAD, CKD, HF	85/male/DM, dyslipidaemia, CAD, HF	63/female/HPT, dyslipidaemia, AF, HF	83/male/HPT, dyslipidaemia, DM, HF	53/female/HPT, DM, dyslipidaemia, CKD, HF
LVEF	20%	20%	–	18%	35%
Medications	Atorvastatin 40 mg o.d., Sacubitril/valsartan 49/51 mg b.i.d.	Rosuvastatin 10 mg o.d., Sacubitril/valsartan 97/103 mg b.i.d.	Atorvastatin 40 mg o.d., Sacubitril/valsartan 24/26 mg b.i.d.	Atorvastatin 40 mg o.d., Sacubitril/valsartan 24/26 mg b.i.d.	Sacubitril/valsartan (unspecific dose)
Clinical presentation	Myalgia, malaise, oliguria,	Muscle weakness, oliguria, SOB	Generalized weakness, malaise, dark urine	Muscle weakness, myalgia, dark urine	Generalized weakness, dark urine
Serum creatinine/LFT on admission	Elevated/deranged ALT, AST, CK	Elevated/deranged ALT, CK	Baseline/deranged ALT, AST, CK	–/deranged ALT, AST, CK	Elevated/deranged ALT, AST, CK
Therapeutic intervention	Discontinuation of medication, IV fluid therapy, RRT, Inotropic support	Discontinuation of medication, IV fluid therapy, inotropic support	Discontinuation of medication, IV fluid therapy	Discontinuation of medication, IV fluid therapy	Discontinuation of medication, IV fluid therapy, inotropic support
Outcome	Recovered/restarted on rosuvastatin 5 mg daily and sacubitril/valsartan 24 mg/26 mg twice daily	Recovered	Recovered/restarted on rosuvastatin 5 mg daily, no plan to restart sacubitril/valsartan	Recovered/restarted on irbesartan	Recovered

AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery diseases; CK, creatinine kinase; CKD, chronic kidney diseases; DM, diabetes mellitus; HF, heart failure; HPT, hypertension; LFT, liver function test; LVEF, left ventricular ejection fraction; SOB, shortness of breath.



values of 14 for cardiovascular death or hospitalization for HF and 21 for all-cause mortality.<sup>18</sup> Our team initially intended that the patient benefit from the reduction in hospitalization for HF, hence the addition of sacubitril/valsartan therapy. The suggested approach for starting sacubitril/valsartan is initiation at the label-recommended dose or less, with up-titration every 2–4 weeks to the target dose, as tolerated by the patient. Conservative approaches to up-titration over 6 weeks were recommended for the population predisposed to adverse effects. Thus, the clinician should monitor for adverse effects such as hypotension, angio-oedema, hyperkalaemia, and deranged renal profiles.<sup>19</sup>

We highlight the importance of the managing physician's awareness of the possibility of drug–drug interaction between sacubitril/valsartan and atorvastatin. To that end, we have outlined an approach for when these medications are to be co-prescribed. We suggest the commencement of low-dose atorvastatin (20 mg daily) in combination with low-dose sacubitril/valsartan (24 mg/26 mg twice daily). The managing physician should follow-up with the patient within 2 weeks after the initiation of treatment to review clinical symptoms, renal and liver profiles, and serum CK. If the patient tolerates the medications, the physician may consider titrating the sacubitril/valsartan to an optimal dose of 97/103 mg twice daily over 6 weeks. The

**Table 3** Pharmacokinetic of statins and sacubitril<sup>15,20–23</sup>

Statins	Dosage/efficacy (serum LDL reduction, %)	Cmax (h)	Metabolism	Elimination
Atorvastatin	High intensity <sup>a</sup> : 40–80 mg Moderate intensity <sup>b</sup> : 10–20 mg Efficacy: 50% serum LDL reduction for Atorvastatin 40 mg	1–2	CYP3A4	Predominately bile (GI); renal <2%
Rosuvastatin	High intensity <sup>a</sup> : 20–40 mg Moderate intensity <sup>b</sup> : 5–10 mg Efficacy: 63% serum LDL reduction for Rosuvastatin 40 mg	3–5	CYP2C9	Predominately bile (GI); renal 10%
Simvastatin	Moderate intensity <sup>b</sup> : 20–40 mg/ Efficacy: 41% serum LDL reduction for Simvastatin 40 mg	4	CYP3A4	Predominately bile (GI); renal 13%
Pravastatin	Moderate intensity <sup>b</sup> : 40–80 mg Efficacy: 34% serum LDL reduction for Pravastatin 40 mg	1–1.5	Non-CYP	Predominately bile (GI); renal 20%
ARNI				
Sacubitril/valsartan	Initial dose: 24 mg/26 mg b.i.d. <sup>c</sup> OR 49 mg/51 mg b.i.d. <sup>d</sup> Optimal dose: 97 mg/103 mg b.i.d.	Sacubitril : 0.5 LBQ657: 2	Esterase	Renal 52%; GI 48%

ARNI, angiotensin receptor neprilysin inhibitor; Cmax, time of the drug is present at the maximum concentration in serum; CYP, cytochrome P; GI, gastrointestinal; LBQ657, active metabolite of sacubitril.

<sup>a</sup>High intensity: reduce low-density lipoprotein (LDL) by  $\geq 50\%$ .

<sup>b</sup>Moderate intensity: reduce LDL by 30–50%.

<sup>c</sup>Reduced initial doses: for renal impairment with eGFR <30; chronic liver diseases with Child-Pugh B.

<sup>d</sup>Recommended initial doses: for all chronic heart failure.

up-titration of atorvastatin to an optimal dose of 40–80 mg daily could be guided by the desired reduction in serum LDL. In the event of muscle-related toxicity, the physician may consider cessation of atorvastatin. In terms of cardiovascular mortality, the patients with HF would likely benefit more from an optimal dose of sacubitril/valsartan than from a statin, as evidenced by NNTs of 14 and 72, respectively.<sup>17,18</sup> The suggested approach is in our favour, as our patient would benefit from the additional reduction in HF hospitalization. In cases where dyslipidaemia is the major concern, the physician may consider rosuvastatin as an alternative to atorvastatin because rosuvastatin may interact less with sacubitril. The plausible mechanism is that rosuvastatin and sacubitril reach maximum serum concentrations at 5 and 2 h after dosage, respectively.<sup>20,21</sup> At 5 h, rosuvastatin is at its peak serum concentration and may experience a lesser inhibitory effect on its elimination by sacubitril, as sacubitril reaches its peak inhibitory effect at 2 h.<sup>12,15</sup> Further research and evaluation of the risks and possible interactions between these two drugs may be useful in identifying the likelihood of rhabdomyolysis and its management.

## Conclusion

We conclude that the co-administration of sacubitril/valsartan and atorvastatin may increase the risk of statin-induced muscle toxicity. We recommend that the physician consider initiating low-dose atorvastatin (20 mg daily) in combination with low-dose sacubitril/valsartan (24 mg/26 mg twice daily). These medications can be titrated gradually to optimal dosages with close monitoring of CK and liver and renal function. If an adverse event develops, cessation of atorvastatin or switching to low-dose rosuvastatin in combination with sacubitril/valsartan should be considered.

## Lead author biography



Dr Kelvin Shenq Woei Siew completed his medical education at the University of Malaya School of Medicine in 2018. He went into training as a clinical researcher in the Department of Cardiology, University Malaya Medical Centre. He is passionate about clinical research in heart failure and non-ischaemic cardiomyopathies. He presented his preliminary work at the ESC Heart Failure Congress 2019, in Athens,

Greece, and the National Heart Association of Malaysia Congress 2019. At present, he is serving as a medical doctor in Malaysia.

## Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** None declared.

**Funding:** None declared.

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