



Rhabdomyolysis in an Increasingly Common Heart Failure Patient for Internists

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Disclosures

- There are no conflicts or disclosures
- The patient had provided consent to this case report

Meet Mr. Jones...

83M who presented with myalgias

Past Medical History:

1. Recent diagnosis of non ischemic dilated cardiomyopathy with EF of 18%, NYHA II baseline
2. Dyslipidemia
3. Hypertension
4. Type 2 Diabetes Mellitus
5. Chronic Thrombocytopenia

Medications:

1. ASA
2. Metoprolol
3. Irbesartan
4. Spironolactone
5. Atorvastatin
6. Metformin/Gliclazide

Meet Mr. Jones...

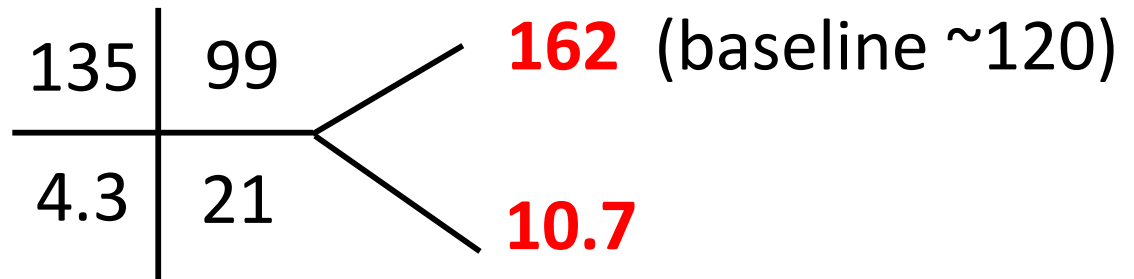
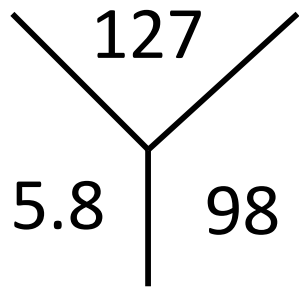
September 2018						
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1. Irbesartan switched to sacubitril/valsartan
2. Progressive myalgias from walking to cane to almost bed bound due to lethargy and weakness
3. Presented to hospital due to fall

Physical Exam:

- Afebrile but tachycardic
- CNS: Normal CN. 4/5 strength in quadriceps/knees, otherwise normal including reflexes
- CVS: Elevated JVP, normal HS
- No rash, compartment syndrome or foci of infection

Investigations:



CK: 16500

Bili: 42

Top HS: 300 → 382

TSH: Normal

Troponin I: -ve

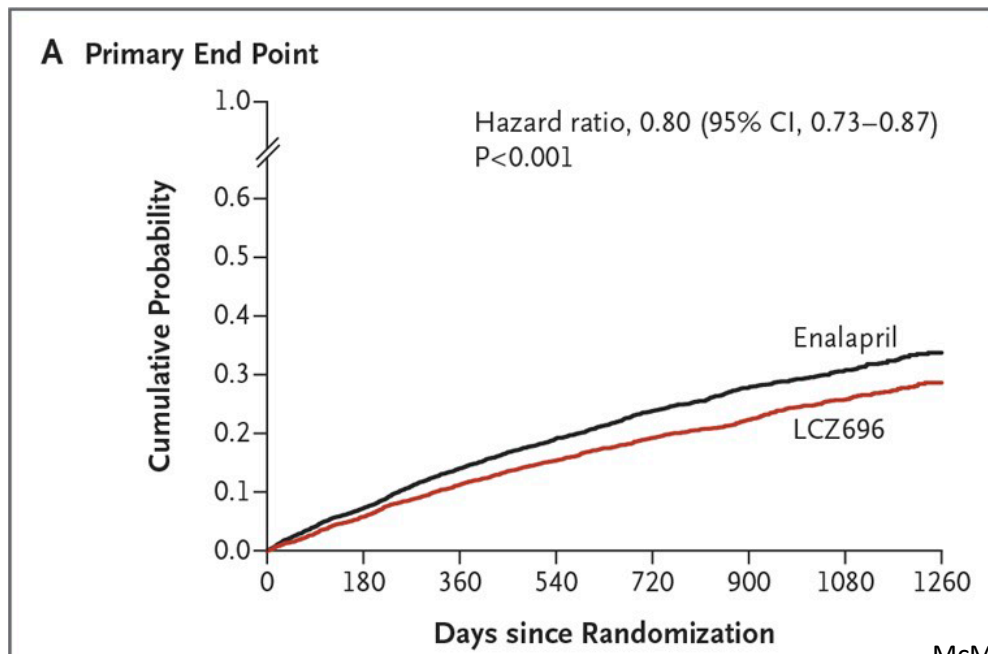
Urinalysis: Hematuria on dipstick, negative RBC on microscopy. Granular casts



Why did this gentleman with CHF get
Rhabdomyolysis?

Increasingly Common CHF Patient:

- Sacubitril/Valsartan has been approved by FDA and Health Canada since 2015
- 2017 CCS Guidelines recommend its use in patients who remain symptomatic despite appropriate goal-directed medical therapy

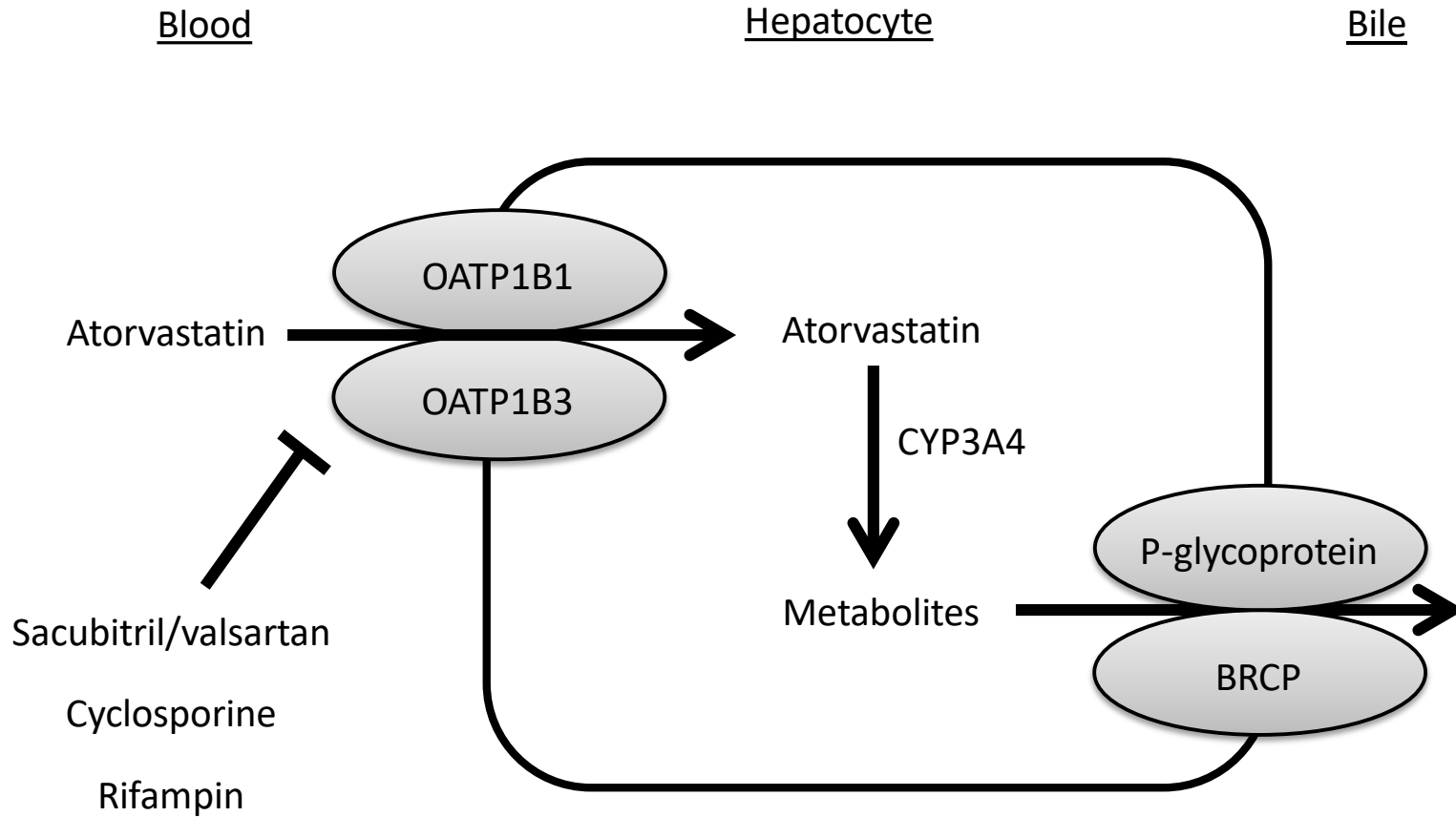


Adverse Effects:

- No mention of rhabdomyolysis as a side effect in PARADIGM-HF
- 60% of patients had ischemic cardiomyopathy and presumably, would have been on a statin

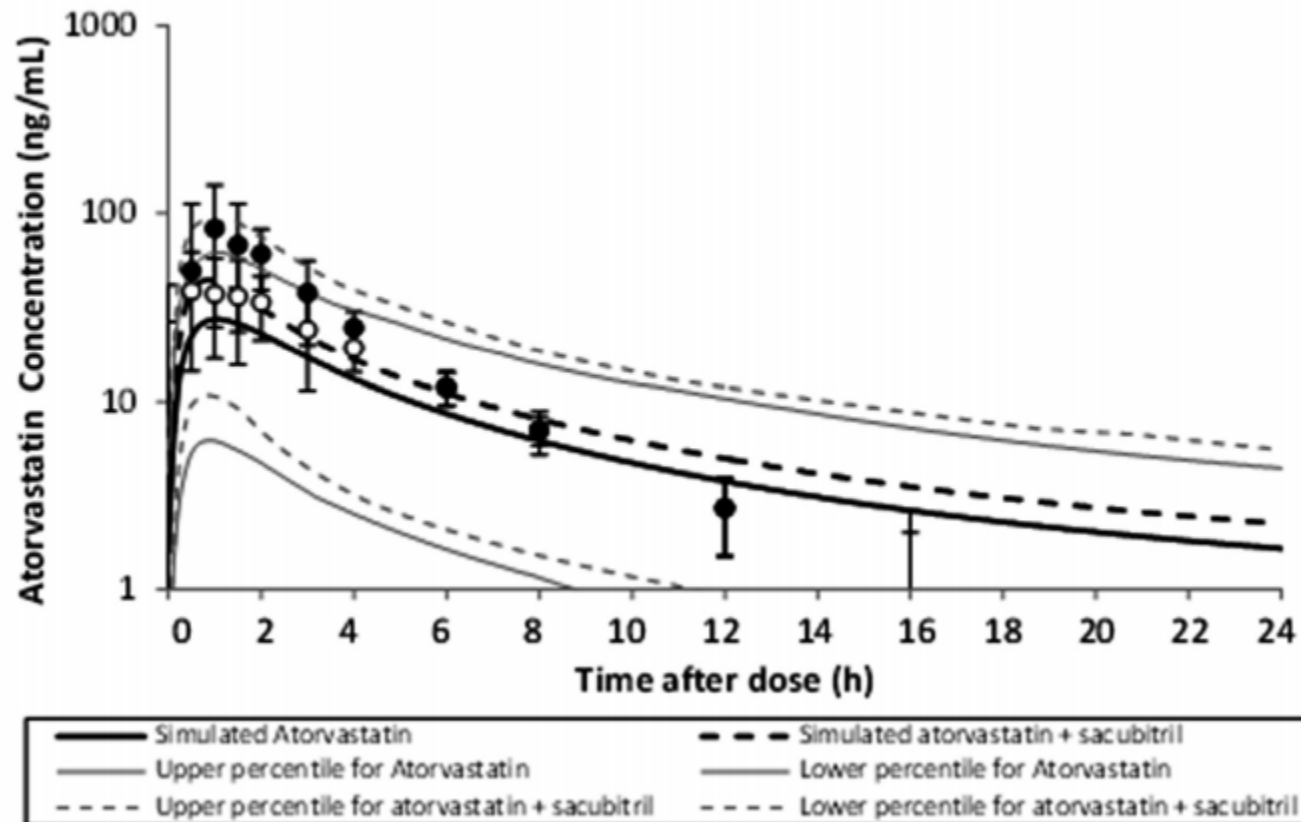
Preferred term	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Number of patients with at least one AE	3419 (81.35)	3503 (82.83)	6922 (82.09)
Hypotension	740 (17.61)	506 (11.97)	1246 (14.78)
Cardiac failure	730 (17.37)	832 (19.67)	1562 (18.52)
Hyperkalaemia	488 (11.61)	592 (14.00)	1080 (12.81)
Renal impairment	426 (10.14)	487 (11.52)	913 (10.83)
Cough	369 (8.78)	533 (12.60)	902 (10.70)
Dizziness	266 (6.33)	206 (4.87)	472 (5.60)
Atrial fibrillation	251 (5.97)	236 (5.58)	487 (5.78)
Pneumonia	227 (5.40)	237 (5.60)	464 (5.50)
Oedema peripheral	215 (5.12)	213 (5.04)	428 (5.08)
Dyspnoea	213 (5.07)	306 (7.24)	519 (6.16)

Mechanism of Adverse Effect:



Why Atorvastatin?

Semi-log plot

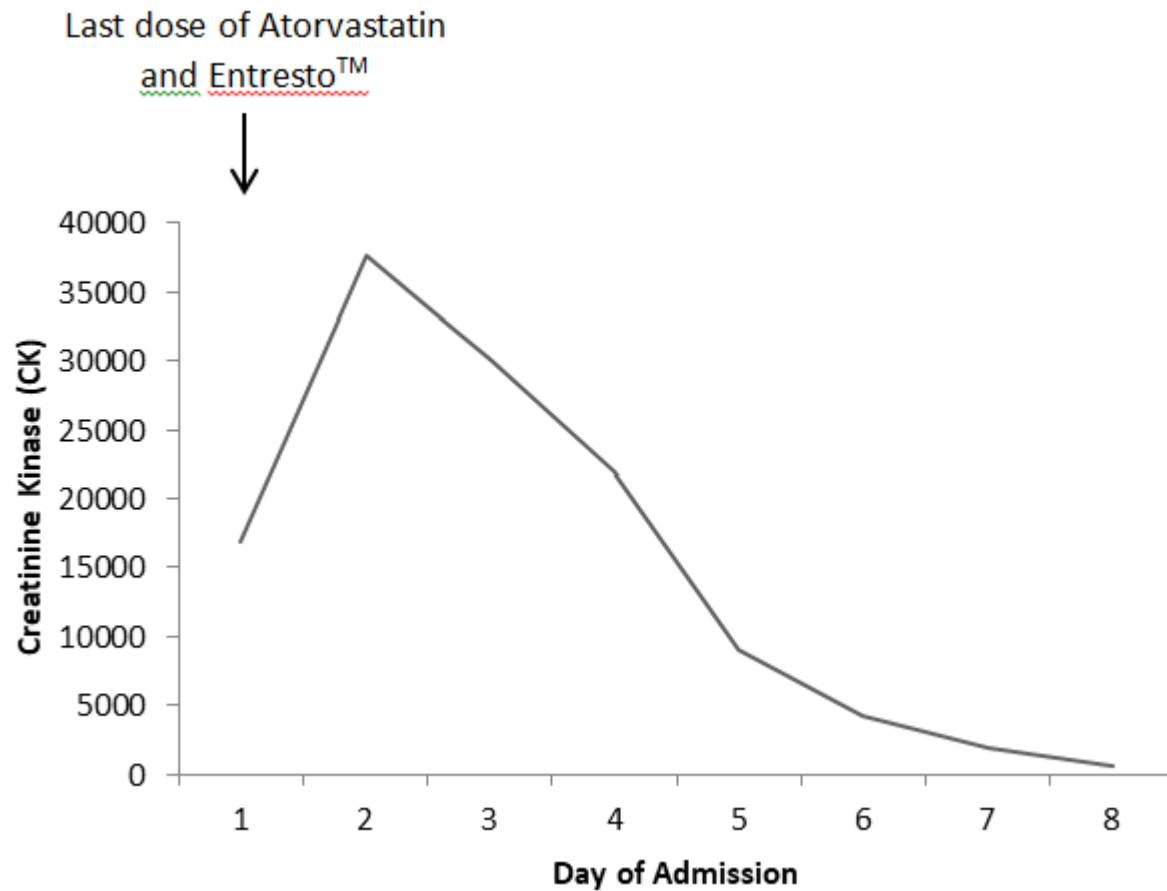


Clinical Implications:

- Other statins metabolized through OATP, but pharmacokinetics do not align with maximum concentration for possible adverse effects
- ? Alter the dosing timing, or consider other statins
- Importance for understanding this risk when co-prescribing this medication and counselling patients accordingly



Back to Mr. Jones



Objectives:

1. Recognize the increasing importance of evaluating for drug interactions in complex patients with new presentations
2. Identify rhabdomyolysis as a potential drug interaction when prescribing sacubitril/valsartan with statins, and the role that information technology played to find the mechanism
3. Apply the underlying pharmacokinetic mechanism to provide alternatives when co-administration is required



Questions?

References:

1. Lin W, Ji T, Einolf H, Ayalasomayajula S, Lin TH, Hanna I, et al. Evaluation of Drug-Drug Interaction Potential Between Sacubitril/Valsartan (LCZ696) and Statins Using a Physiologically Based Pharmacokinetic Model. *Journal of pharmaceutical sciences*. 2017;106(5):1439-51.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137-e61.
3. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *The Canadian journal of cardiology*. 2017;33(11):1342-433.
4. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England journal of medicine*. 2014;371(11):993-1004.
5. Ayalasomayajula S, Han Y, Langenickel T, Malcolm K, Zhou W, Hanna I, et al. In vitro and clinical evaluation of OATP-mediated drug interaction potential of sacubitril/valsartan (LCZ696). *Journal of clinical pharmacy and therapeutics*. 2016;41(4):424-31.
6. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *British journal of pharmacology*. 2009;158(3):693-705.