UMFT
Universitatea de Medicină și Farmacie „Victor Babeș” din Timișoara

LUND UNIVERSITY

CELL-PERMEABLE SUCCINATE BYPASSES STATIN-INDUCED MITOCHONDRIAL COMPLEX I INHIBITION IN HUMAN PLATELETS

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Disclosures

- I have no disclosures

What are statins?

- Statins are a group of lipid lowering medications known as HMG-CoA reductase inhibitors
- They are first line medication in the treatment of Hypercholesterolemia

Why are they so widely used ?

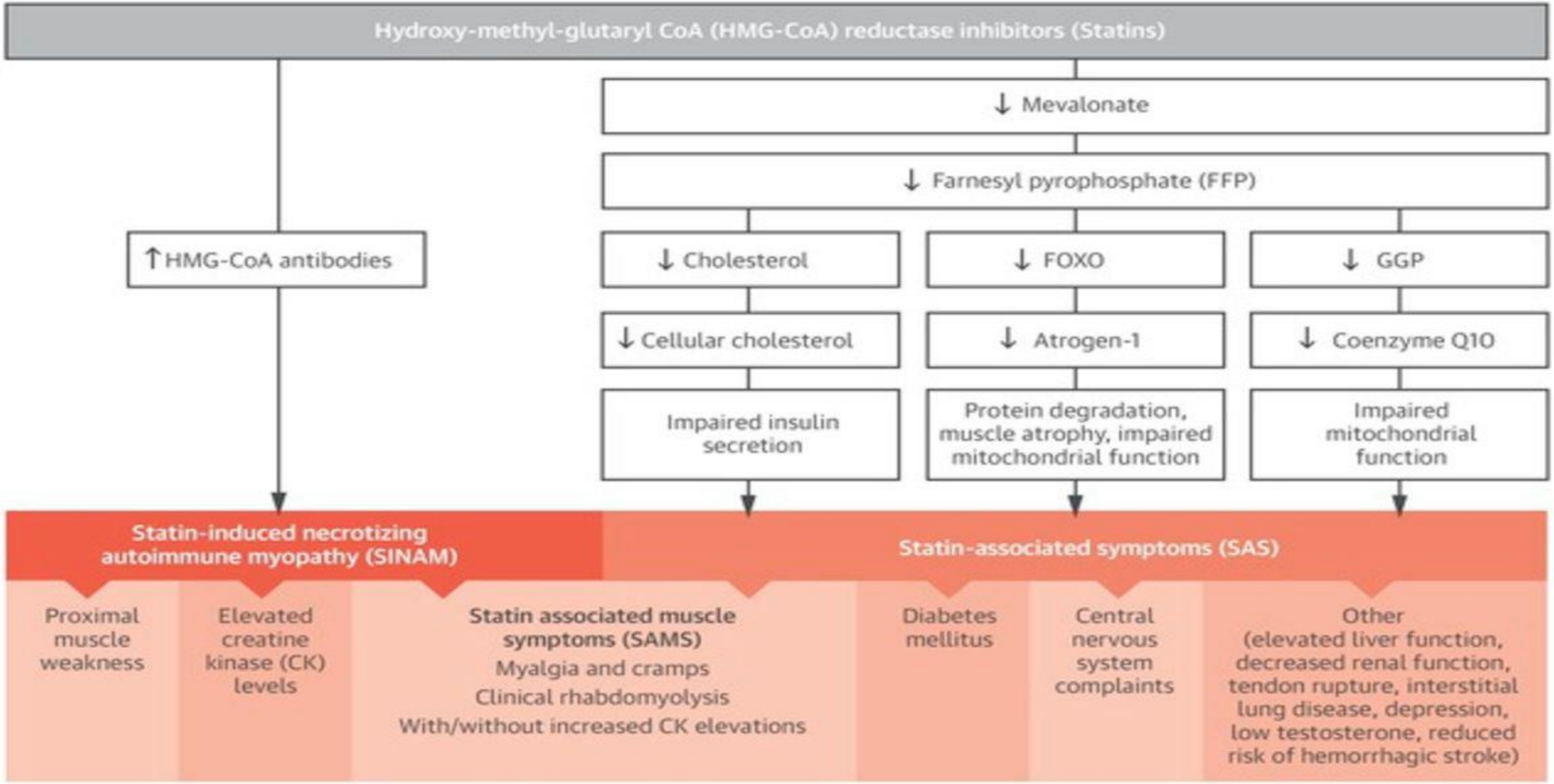
Recommendations	Class[a]	Level[b]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

- Atheromas regressed to similar degrees in patients with or without diabetes on high-intensity statin therapy
- High-dose statin therapy is more effective than moderate- or low dose regimens to halt progression of atherosclerosis
- Diabetic patients require fairly aggressive lipid therapy to get the same results as in nondiabetic patients

European Heart Journal.
doi:10.1093/eurheartj/ehw272. 2016

Boscheret S. Intense statin therapy treats atheromas in diabetes. Internal Medicine News. Mar 2013
Nicholls SJ, et al. Effect of Two Intensive Statin Regimens on Progression of Coronary Disease (SATURN). N. Engl. J. Med. 2011;365:2078-87

CENTRAL ILLUSTRATION: Statin-Associated Side Effects



Thompson, P.D. et al. J Am Coll Cardiol. 2016;67(20):2395–410.

Statin-induced changes in mitochondrial function

- Disturbances in mitochondrial quantity and quality have been cited
- Decreased respiratory rates in intact platelets with unchanged respiratory capacity in rat platelets
- Reduction in NADH-linked respiration in human permeabilized platelets
- Decreased mitochondrial CII, CIII and CIV activity in muscle cells

Neeltje A.E. Allard, M.D., M.Sc., Tom J.J. Schirris, Ph.D., Rebecca J. Verheggen, M.D., M.Sc., Frans G.M. Russel, Ph.D., Richard J. Rodenburg, Ph.D., Jan A.M. Smeitink,Ph.D., Paul D. Thompson, Ph.D., Maria T.E. Hopman, M.D., Ph.D., and Silvie Timmers, Ph.D - Statins affect skeletal muscle performance: evidence for disturbances in energy metabolism The Journal of Clinical Endocrinology & Metabolism Endocrine Society
Vevera J, Z. Fišar Z, Nekovářová T, Vrablík M, Zlatohlávek L, Hroudová J, Singh N, Raboch J, Valeš K. (2016). Statin-induced changes in mitochondrial respiration in blood platelets in rats and humans with dyslipidemia. Physiol. Res; 65: 777-788

Cerivastatin

- Was taken out of use due to a large number of cases of statin-induced rhabdomyolysis

- It has been shown to be toxic to mitochondria

James M.McKenneyPeterGanzBarbara S.WigginsJoseph S.Saseen Clinical Lipidology A Companion to Braunwald's Heart Disease 2009, Pages 253-280 https://doi.org/10.1016/B978-141605469-6.50026-3
Yvonne Will & James Dykens (2014) Mitochondrial toxicity assessment in industry – a decade of technology development and insight, Expert Opinion on Drug Metabolism & Toxicology, 10:8, 1061-1067, DOI: 10.517/17425255.2014.939628
Radha Ramachandran and Anthony S. Wierzbicki Statins, Muscle Disease and Mitochondria, *J. Clin. Med.* 2017, *6*(8), 75; https://doi.org/10.3390/jcm6080075

Cell-permeable succinate prodrugs

- Increased Succinate-linked respiration in intact platelets with CI inhibition
- Attenuated lactate production
- Metabolomics confirms metabolism of delivered succinate

Ehinger JK, Piel S, Ford R, Karlsson M, Sjövall F, Åsander Frostner E, Morota S,Taylor RW, Turnbull DM, Cornell C, Moss SJ, Metzsch C, Hansson MJ, Fliri H, Elmer E. Cell-permeable succinate prodrugs bypass mitochondrial complex I deficiency (2016). Nat Commun.7:12317

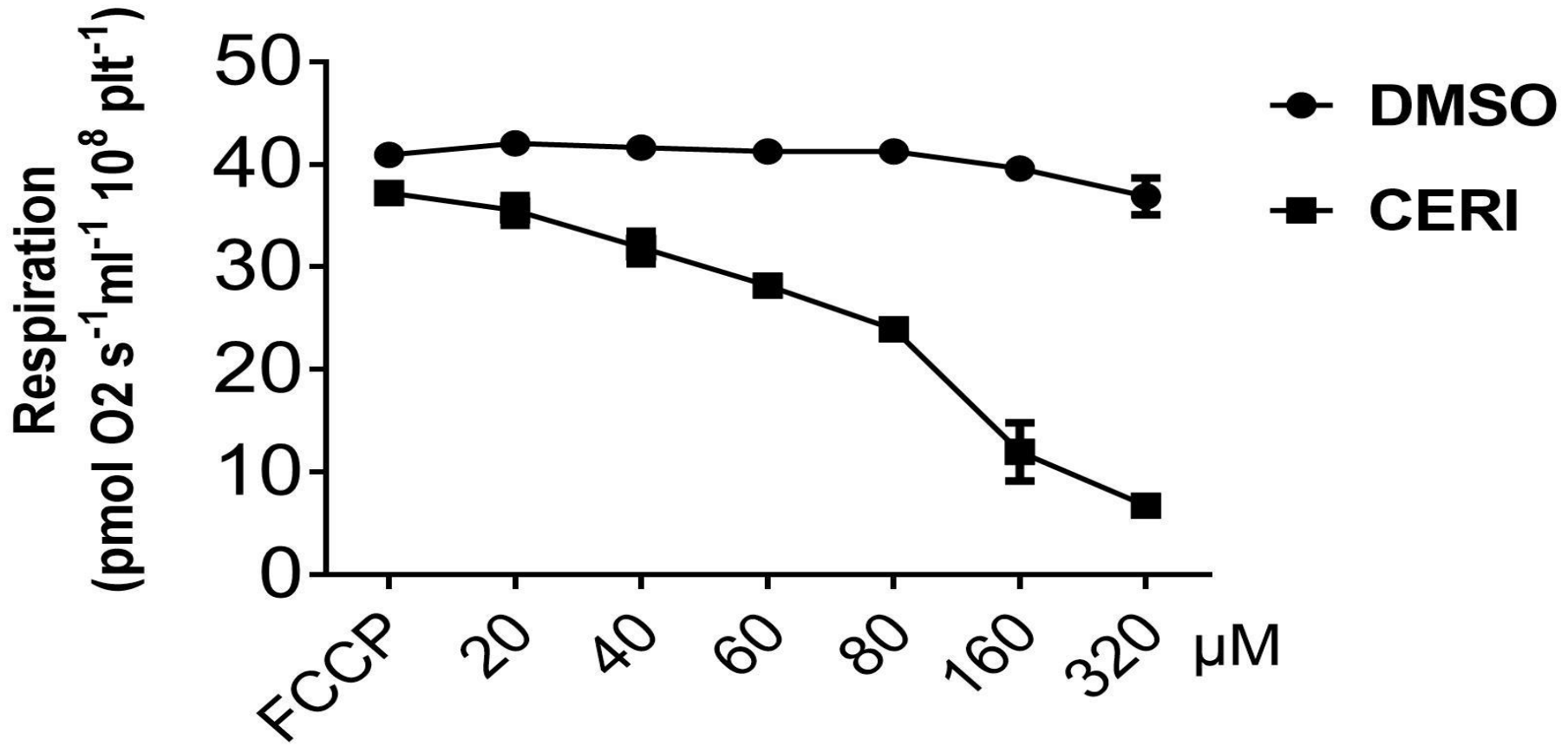
Aim of the study

- To assess the effects of two statins on platelet mitochondrial respiration in human platelets in the presence *vs.* the absence of NV118, a cell-permeable succinate prodrug

Materials and Methods

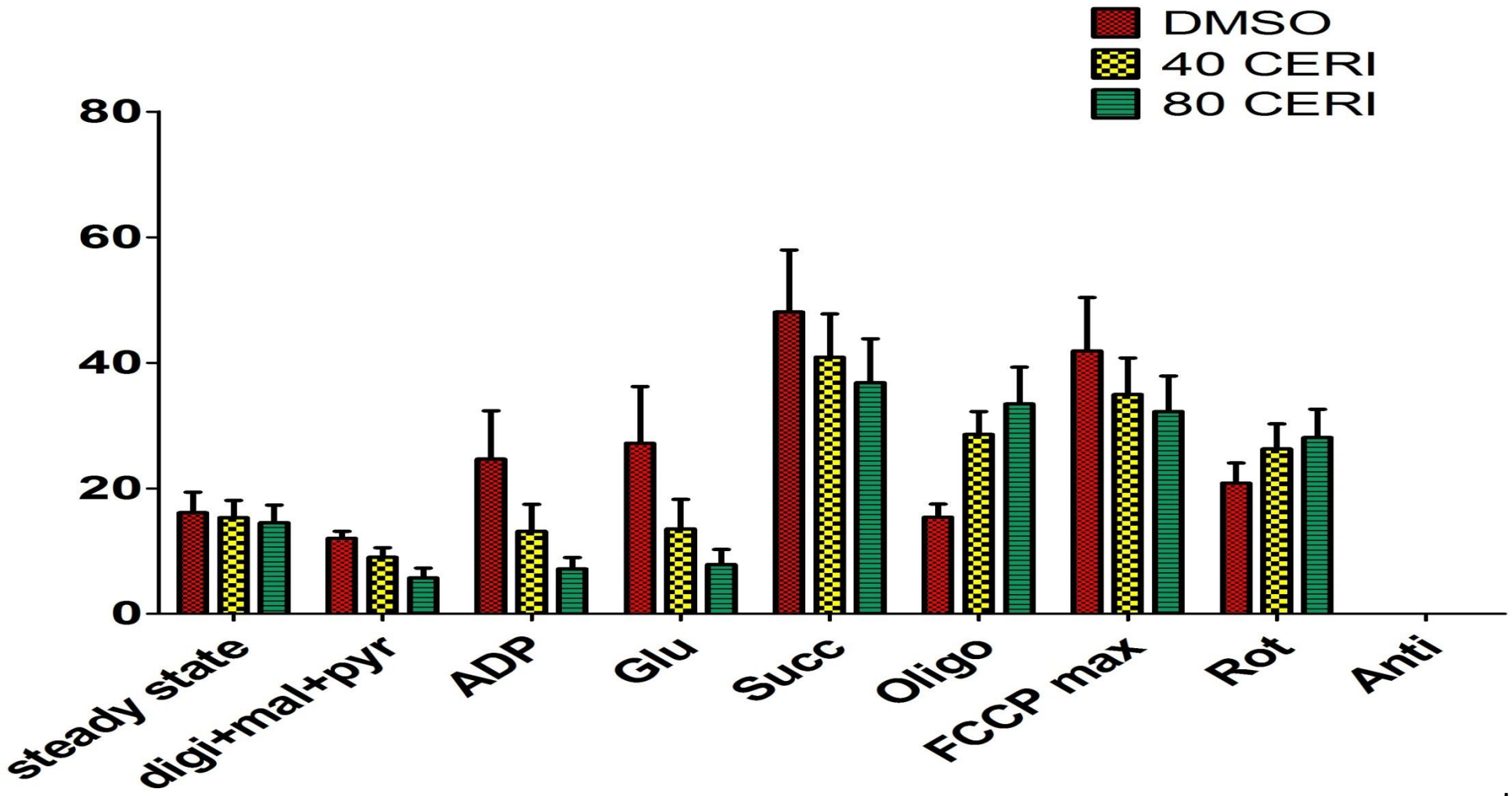
- High-resolution respirometry (OROBOROS - O2k)
- Peripheral blood platelets isolated from healthy volunteers
- Buffer MIR05
- SUIT protocols following acute incubation with cerivastatin

Dose-titration for the assessment of impairement of mitochondrial respiration



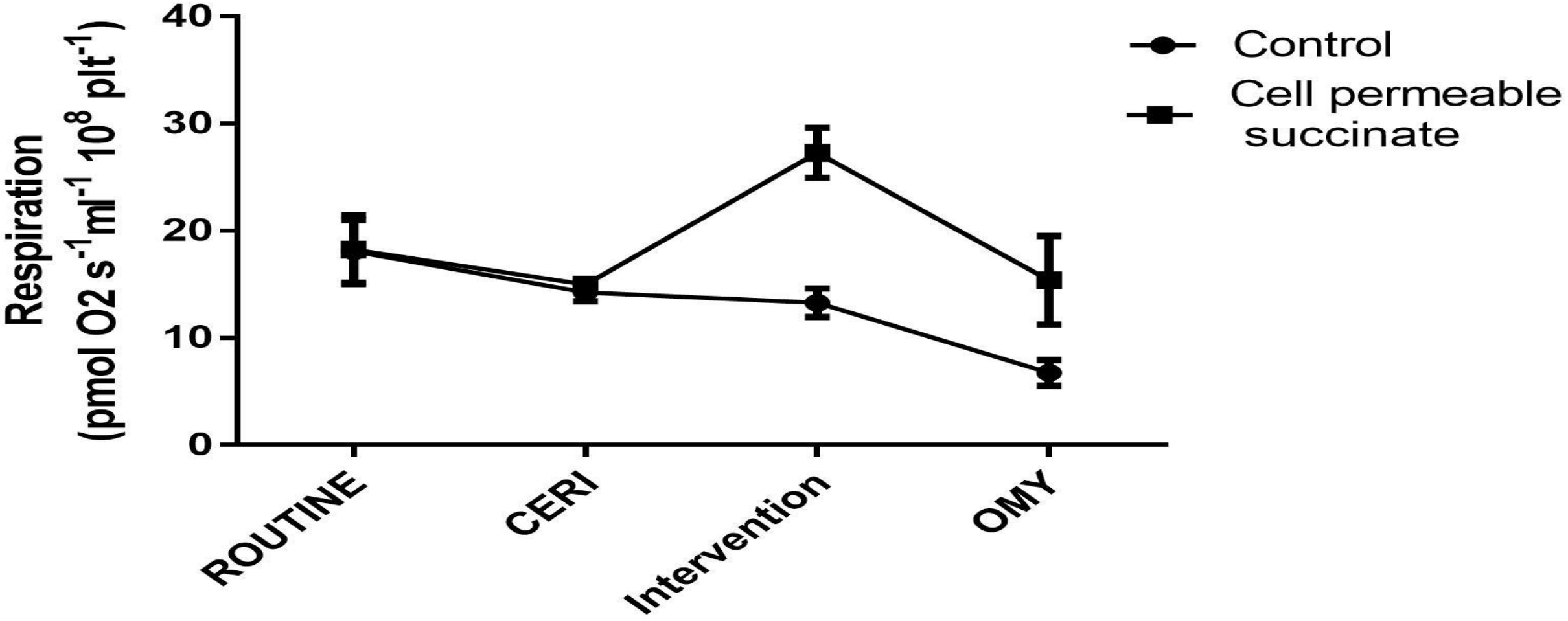
Unpublished data

Dose-dependent impairement of mitochondrial respiration in permebilized platelets



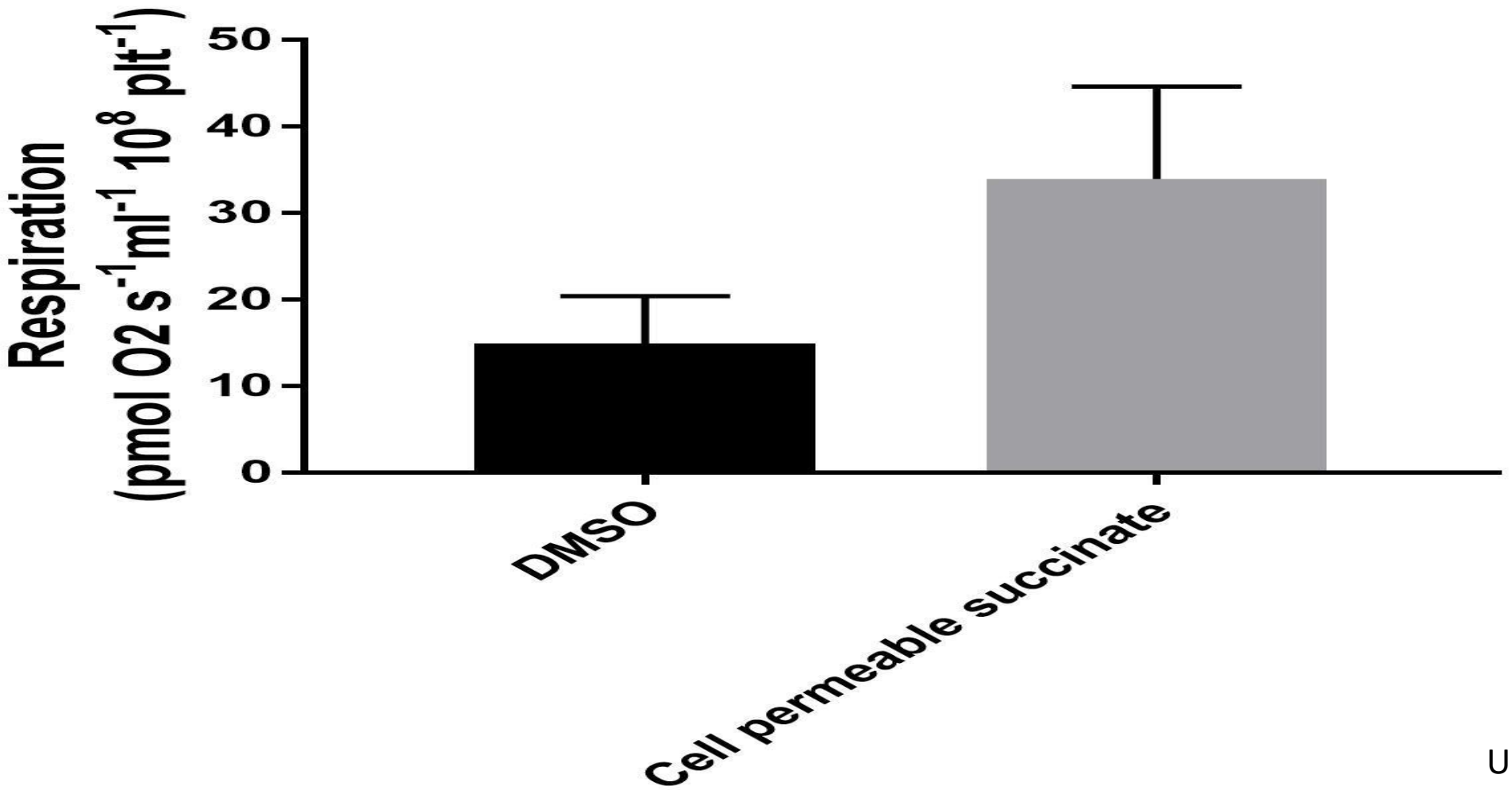
Unpublished data

OMY effect on Cerivastatin-treated plateles *vs.* control



Unpublished data

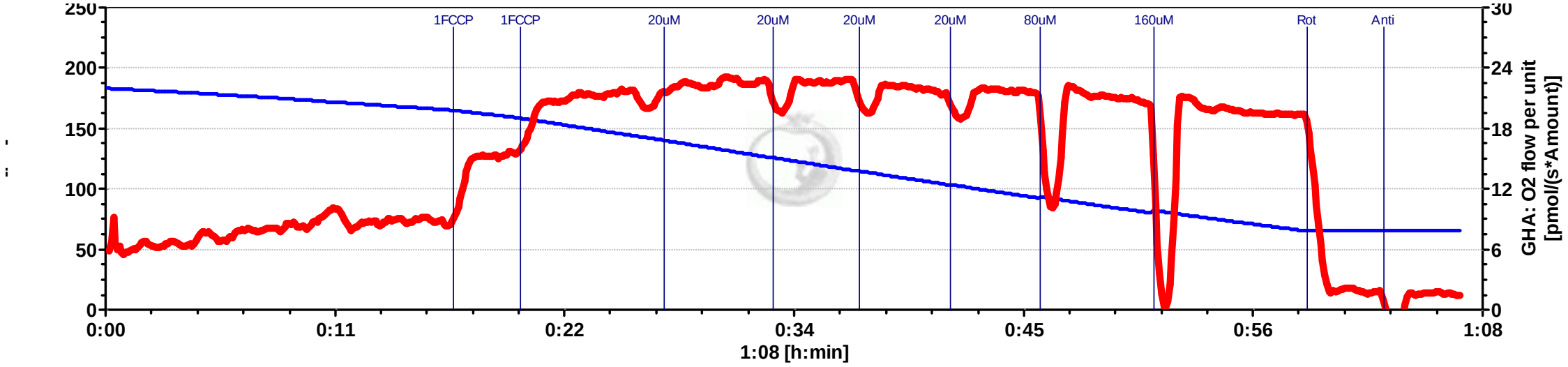
FCCP max Cerivastatin - treated plateles *vs.* control



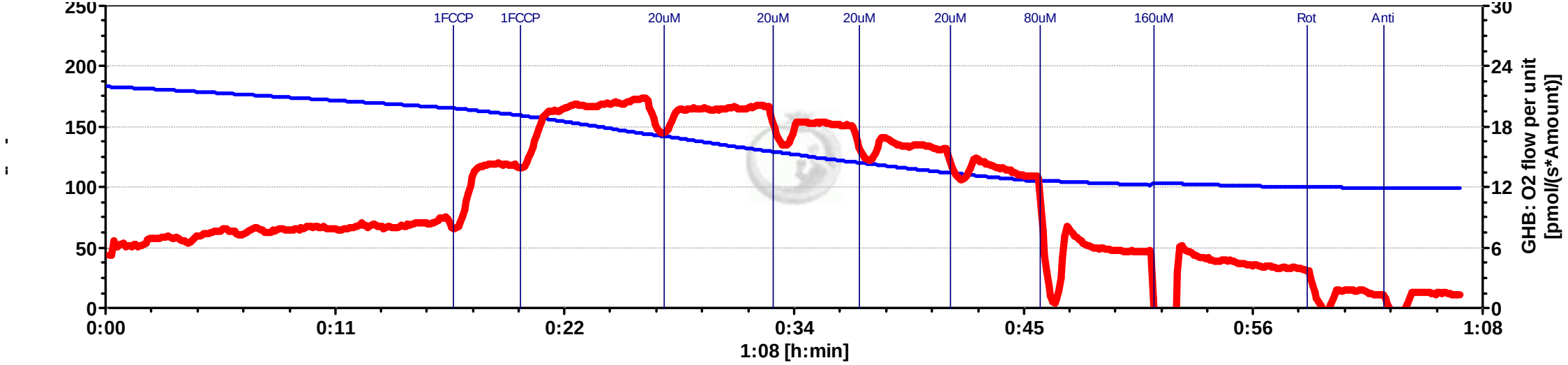
Unpublished data

Cerivastatin-induced dose-dependent decrease in respiration – Typical trace

DMSO

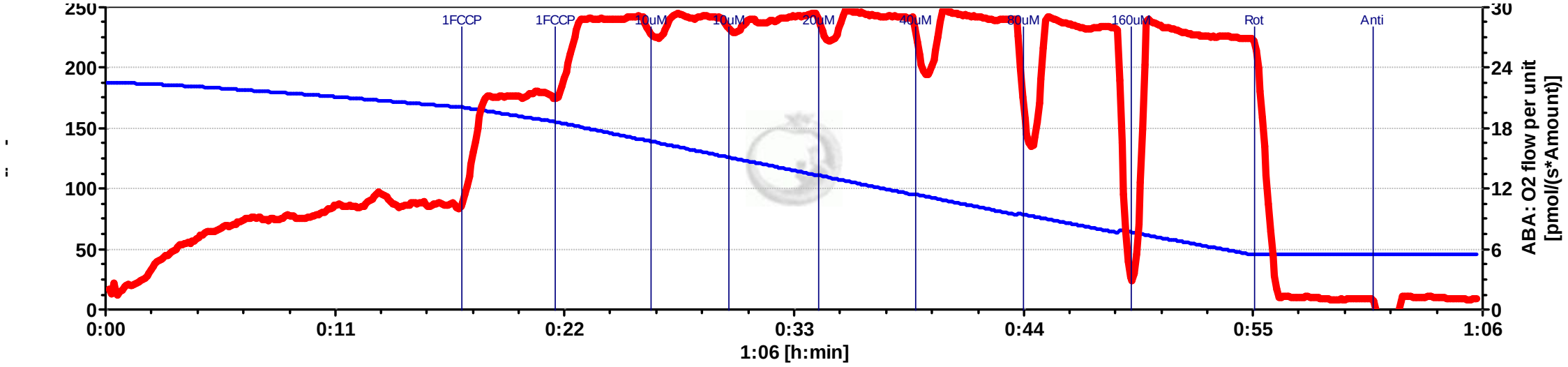


Cerivastatin

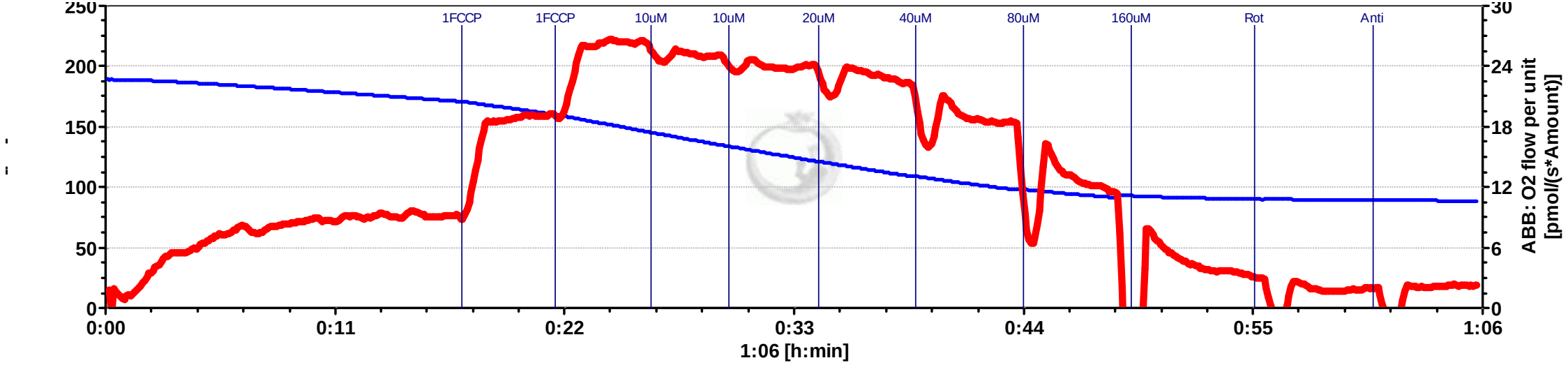


Atorvastatin-induced dose-dependent decrease in respiration – Typical trace

DMSO

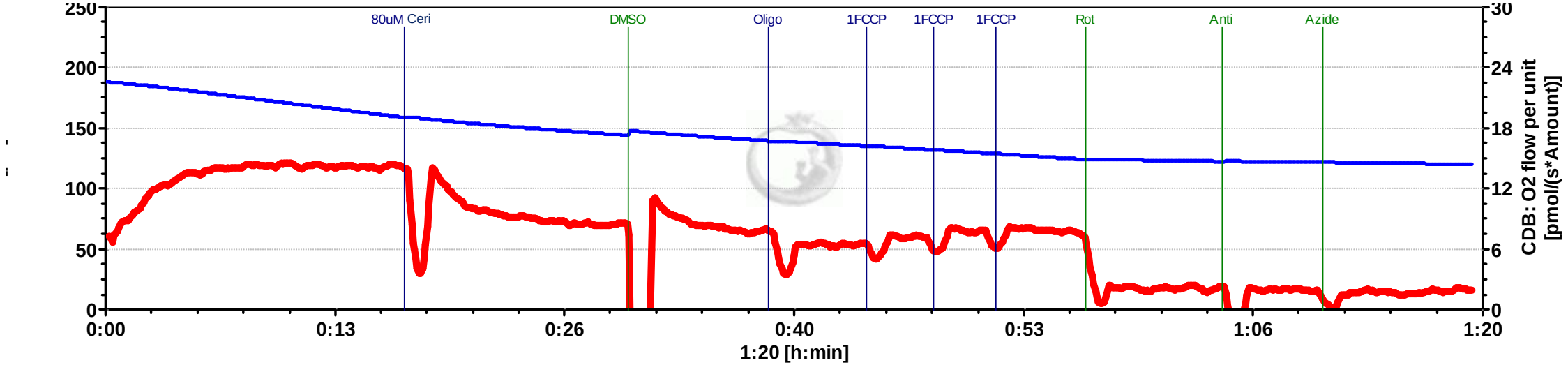


Atorvastatin

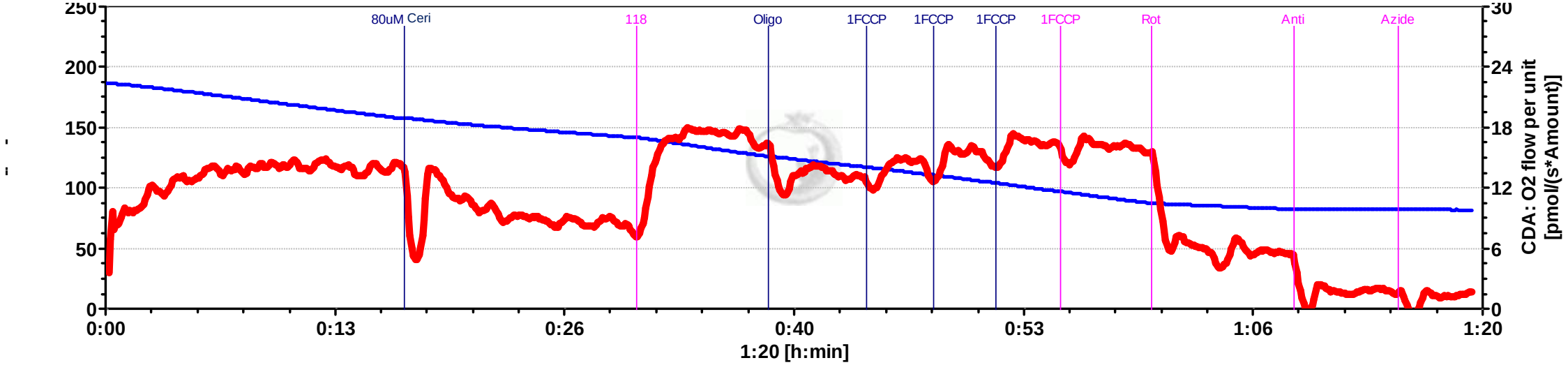


Cell-permeable succinate bypassed Cerivastatin-induced mitochondrial CI inhibition and alleviated the repsiratory deficit - Typical trace

Control

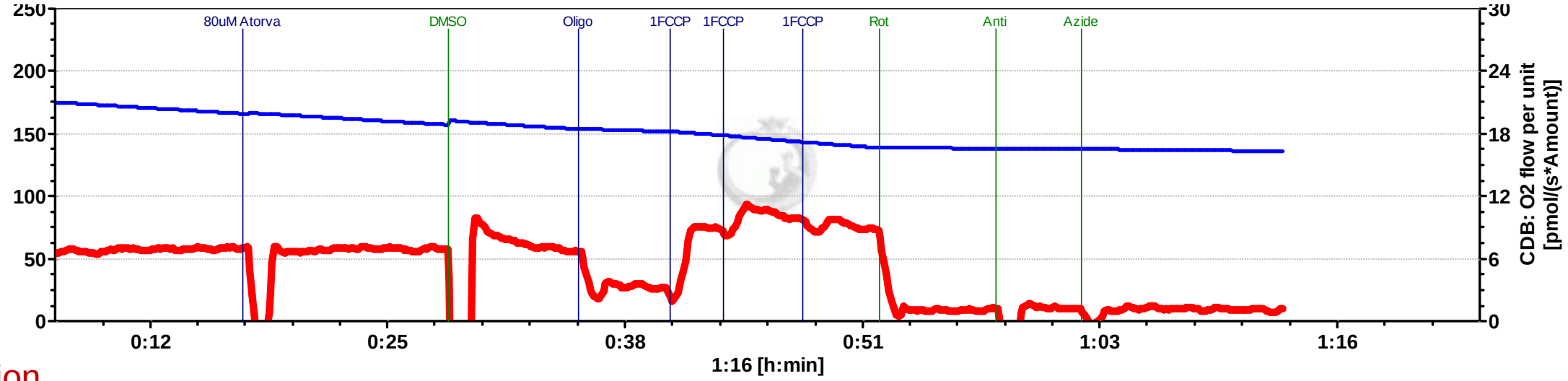


Intervention

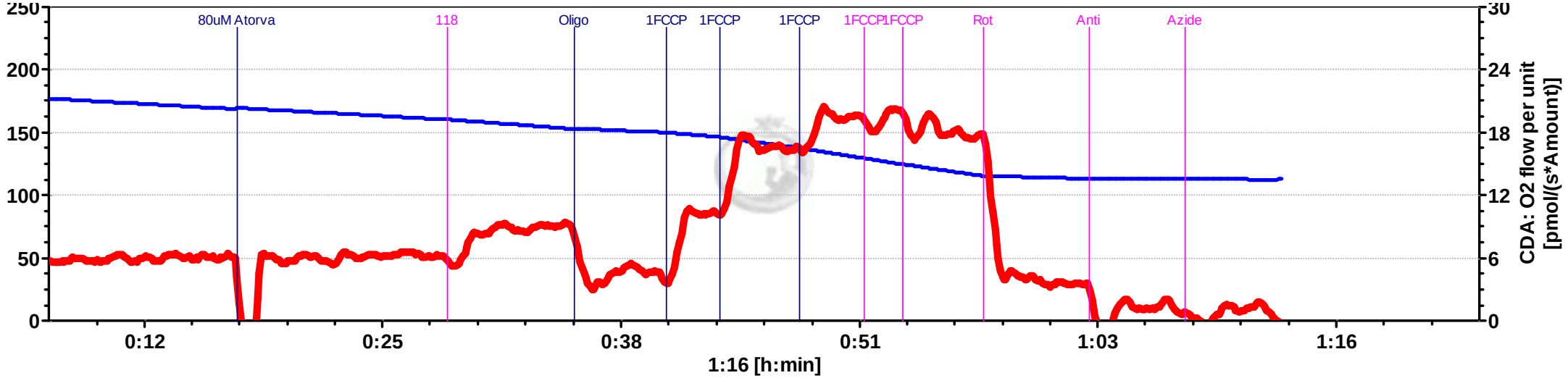


Cell-permeable succinate bypassed Atorvastatin-induced mitochondrial CI inhibition and alleviated the respiratory deficit - Typical trace

Control



Intervention



VARIOUS STATIN DRUG INTERACTIONS

NTERACTION TYPE	STATIN SUBSTRATES	COMMON INHIBITORS OF CYP450 PATWAY OR TRANSPORTER SYSTEM => ↑ statin blood level	COMMON INDUCERS OF CYP450 PATWAY OR TRANSPORTER SYSTEM => ↓ statin blood level
CYP450 Drug Interactions With Statins			
CYP2C9	fluvastatin, **rosuvastatin**, pitavastatin	azole antifungals; amiodarone; gemfibrozil	Rifampicin, phenobarbital, phenytoin
CYP3A4	**atorvastatin**, lovastatin, **simvastatin**	azole antifungals; amiodarone; azithromycin; erythromycin; clarithromycin; fluvoxamine; fluoxetine; sertraline; cyclosporine; tacrolimus; sirolimus; diltiazem; verapamil; protease inhibitors; grapefruit juice; posaconazole; ticagrelor, tricyclic antidepressants	Phenytoin, phenobarbital, barbiturates, rifampicin; omeprazole; carbamazepine
Transporter Proteins And Statins			
OATP1B1	**atorvastatin**, pitavastatin, pravastatin, **rosuvastatin**, **simvastatin**	carbamazepine, clarithromycin, cyclosporine, erythromycin, gemfibrozil, protease inhibitors, roxithromycin, rifampin, sildenafil, sacubitril, telithromycin	None known at this time
OATP1B3	fluvastatin, pravastatin, **rosuvastatin**	clarithromycin, cyclosporine, erythromycin, rifampin, roxithromycin, rifampin, sacubitril, telithromycin	None known at this time
Pgp-1	**atorvastatin**, lovastatin, pitavastatin, **simvastatin**	amiodarone, atorvastatin, azithromycin, captopril, carvedilol, cimetidine, clarithromycin, colchicine, conivaptan, cyclosporine, diltiazem, azole antifungal drugs, sertraline, tacrolimus, grapefruit juice	Carbamazepine, phenytoin rifampin, St. John's wort

Conclusions

- Acute administration of statins induced a dose-dependent impairement of mitochondrial respiration
- The cell-permeable succinate prodrug alleviated the mitochondrial respiratory defect
- The cell-permeable succinate prodrug bypassed the mitochondrial dysfunction induced by statins

Future direction

Further investigation of platelets isolated from patients chronically treated with statins in the presence vs the absence of the prodrug is envisaged.

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Thank you!