Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES
October 2020, Volume 14, Number 4

Research Paper:

Carvedilol: A Promising Drug Combined With Lipid-lowering Medications for Patients With Hypertension and Heart Failure

Mohsen Zabihi[1*], Fatemeh Askarian[1], Seyed hossein Hekmati Moghaddam[2], Majid Rajaee[3]

1. Pharmaceutical Research Center, School of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
2. Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
3. Department of Pharmaceutics, School of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran.

Use your device to scan and read the article online

How to cite this paper Zabihi1 M, Askarian F, Hekmati Moghaddam SH, Rajaee M. Carvedilol: A Promising Drug Combined With Lipid-lowering Medications for Patients With Hypertension and Heart Failure Iranian Journal of Toxicology. 2020; 14(4):245-252. http://dx.doi.org/10.32598/ijt.14.4.708.1

http://dx.doi.org/10.32598/ijt.14.4.708.1

Article info:
Received: 28 May 2020
Accepted: 01 Sep 2020
Online Published: 01 Oct 2020

*** Corresponding author:**
Mohsen Zabihi, PhD.
Address: *Department of Pharmacology, School of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.*
E-mail: *mzabihi100@gmail.com*

ABSTRACT

Background: Statins frequently cause myopathy especially in combination with fibrates, and physical activity is considered a trigger for the muscle disorder. Elevated plasma levels of creatine kinase (CK), lactate dehydrogenase (LDH) and aldolase, are the main indicators of the severity of myopathy. Carvedilol is commonly used with lipid-lowering drugs in the management of heart failure, hypertension and dyslipidemia. It is not yet clear whether carvedilol, an alpha and β blocker, and anti-oxidant, may influence the development of myopathy when combined with statins and fibrates in cardiac patients.

Methods: In this animal experiment, a 10 days regimen containing oral atorvastatin and gemfibrozil at doses of 80 and 1000 mg/kg/day, respectively, was used to induce myopathy in rats. The animals were forced to swim in a pool on days 8, 9 and 10 into the study. Carvedilol (2.5 mg/kg/day) was added to atorvastatin and gemfibrozil during the 10-day study period, in addition to the exercise protocol given to the treatment groups only. The mean of swimming tolerance times and the serum levels of CK, LDH and aldolase were measured at the completion of the study.

Results: Carvedilol did not significantly alter the swimming tolerance time or the plasma levels of CK, LDH and aldolase in the rats receiving ATV, GMF and carvedilol plus the exercise protocol, compared with those that did not receive carvedilol (P>0.05).

Conclusion: Carvedilol may be used in combination with lipid-lowering drug in the management of patients with heart failure and hypertension, pending its safety approval by clinical studies in humans.

Keywords: Carvedilol, Fibric acids, Muscular disease, Rats, Hydroxymethylglutaryl-CoA reductase inhibitors

Introduction

Lipid-lowering drugs may lead to serious adverse effects such as myopathy. The primary manifestation of myopathy include myalgia and weakness followed in extreme cases of rhabdomyolysis [1, 2]. Rhabdomyolysis is a fatal condition characterized by destruction of skeletal muscle fibers, sometimes accompanied by multiple-organ failure [3].

Statin drugs inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, and are widely used

to prevent and treat cardiovascular diseases resulting from hyperlipidemia [2]. Statins are effective and mostly safe in reducing serum cholesterol level [2]. However, the side effect on muscles remains a considerable risk particularly when statins are consumed simultaneously with fibrates [4]. Muscle injury associated with concurrent statins and fibrate administration are manifested as mild to devastating signs and symptoms [5, 6]. The cellular and molecular basis for persistent myalgia induced by statins is not fully addressed, but may involve metabolic stress on cells. Single-nucleotide polymorphisms have been reported in patients with statin-related myalgia [7]. The risk of muscle injury from statins is dose-dependent, especially for those formulations metabolized primarily by one of the cytochrome P450 enzymes, i.e., CYP3A4 [8].

Measurement of the circulating levels of enzymes at high concentration within striated muscle cells is the simplest way to diagnose and follow up on muscle disease. The single most important of these enzymes is creatine kinase (CK). The highest serum levels of CK occur when skeletal or cardiac muscles are injured. Unaccustomed exercise can also lead to increases in serum CK levels [9]. Another enzyme that is predominantly found in skeletal muscles is aldolase. Its serum level is less specific than that of CK in muscle diseases. Lactate dehydrogenase (LDH) is another marker enzyme for myopathies, but its serum level is commonly increased in a variety of other organ diseases, thus lowering its specificity to myopathy [9].

Carvedilol, a vasodilator and α-1 and β adrenoceptor blocker, is also an antioxidant and free radical scavenger [10-13]. Carvedilol imparts protective effects on skeletal muscle myofibrils in experimental animal models for heart failure [14]. This drug is used routinely in combination with other medications, such as lipid-lowering drugs in patients with cardiovascular conditions. The muscle effects of carvedilol in patients receiving concurrent statins and fibrates are questionable.

This study was conducted with the aim of evaluating the impact of carvedilol on myopathy induced by combined statin and fibrate in rats. Previous observations (unpublished data) have suggested that an experimental protocol consisting of oral atorvastatin (ATV) and gemfibrozil (GMF) combined with vigorous exercise in rats may be an appropriate model for inducing myopathy. Hence our impetus to conduct this study.

Materials and Methods

Animal experiments: Sixty days old, male inbred Wistar rats, weighing 270±20 g, were procured from the animal house at the School of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The animals were kept in separate cages (6 rats per cage), at a room temperature of 20-23°C under 50%-60% relative humidity and 12 hours of alternating light and dark cycles. They had free access to standard rat food pellets and drinking water. All procedures regarding animal care were consistent with the guidelines of care and experiments on laboratory animals as set by the Ethics Committee at Shahid Sadoughi University of Medical Sciences (Certificate #: IR.SSU.MEDICINE.REC.1398.237). Animals were divided randomly into five groups of 12 rats each as follows:

- Group 1, controls without exercise. They received distilled water only.

- Group 2, controls received distilled water for 10 days and were forced to swim on days 8, 9 and 10.

- Group 3 received combined ATV (80 mg/kg/day) and GMF (1000 mg/kg/day) orally without swimming for 10 days.

- Group 4 received the combined ATV and GMF for 10 days and was forced to swim on days 8, 9 and 10.

- Group 5 received the combined ATV, GMF and carvedilol (2.5 mg/kg/day) for 10 day, and was forced to swim on days 8, 9 and 10.

The above drug doses were selected based on our previous pilot experiment (unpublished data).

Exercise Training: The animals were forced to swim in order to perform vigorous exercise, based on the protocol in a previous study [15] with slight modifications. A vertical glass cylinder, 30 cm in diameter and 40 cm height, was used containing water at 25ºC, and the rats were placed in it individually for the purpose of swimming exercises. The duration of exercise, including climbing and swimming from the beginning to the point of near-drowning due to fatigue was recorded by a stop watch. On day 10, the mean duration of rats' swimming over the previous three days was considered as swimming tolerance time.

Chemicals: Atorvastatin calcium (Sobhan Co., Tehran, Iran), gemfibrozil 5-(2,5-dimethylphenoxy)-2,2-dimeth-

ylpentanoic acid (Darupakhsh Co., Tehran, Iran) and carvedilol (Jalinus Co., Tehran, Iran) were purchased from the respective suppliers. The compounds were dissolved in distilled water at predetermined amounts to prepare the drug solutions, which were given to the animal by gavage every morning at 9 a.m.

Serum Enzymes' Assays: Upon general anesthesia with 50 mg/kg of ketamine and 10 mg/kg of xylazine, 3 mL blood samples were collected in tubes containing K2-EDTA, from the rats' hearts at the end of experiments (day 10). The assay for each serum enzyme was performed according to instructions provided by the suppliers' kits. The descriptions of the commercial kits were as follows:

- CK-NAC-LQ kit (Audit Diagnostics, Belfast, Ireland): UV-spectrophotometry, kinetic reaction, 37°C, linearity range 2-2000 U/L.

- LDH kit (Bionik, Tehran, Iran): Stable liquid reagents, UV-spectrphotometry, kinetic reaction, 37°C, linearity range 2-1450 U/L.

- Aldolase kit (Biorex, Fars, Iran): UV-spectrophotometry, kinetic reaction, 37°C, linearity range 1-28 U/L.

Statistical analyses: The parameters that were measured and compared among the groups included: rats' weights; swimming tolerance times; and the serum enzyme levels. One-way analysis of variance (ANOVA) was used for the data analyses, followed by Tukey's post hoc test. The statistical significance level was defined as $P<0.05$.

Results

Rats' body weight: At the completion of the study, there was no significant difference in the body weights of the rats assigned to the five groups ($P\leq0.05$).

Swimming exercise tolerance time: The Mean±SD of swimming tolerance time (days 8, 9 & 10) for the control rats in Group 2 was significantly higher (398±22.6 sec.) than that for those in the experimental Group 4 (285±23.8 sec; $P<0.001$). In Group 5, carvedilol slightly decreased the swimming tolerance time (257±20.4 sec.) compared to that for Group 4 ($P>0.05$). Also, carvedilol in Group 5 significantly decreased the swimming tolerance time compared to that for the controls in Group 2 ($P<0.01$). Figure 1 represents the swimming tolerance time for the rats in the five groups.

Serum creatine kinase: The exercise significantly increased CK levels both in the controls and the two experimental groups that did the swimming exercise (Groups 2, 4 & 5) as compared to the groups that did not do the exercise ($P<0.001$). Likewise, the serum CK levels were significantly higher in Groups 4 and 5 than in the control rats in Group 2 that did the exercise ($P<0.001$). The differences in the CK levels between Groups 1 (controls) and 3, and between the experimental Groups 4 and 5 were not significant (Figure 2).

Serum Lactate Dehydrogenase: The plasma LDH levels were significantly higher in the control Group 2 and the experimental Groups 4 and 5, than in Groups 1 and 3, where rats did not swim ($P<0.001$). There were no significant differences between the LDH levels in Groups 1 and 3, where no exercise was performed. Also

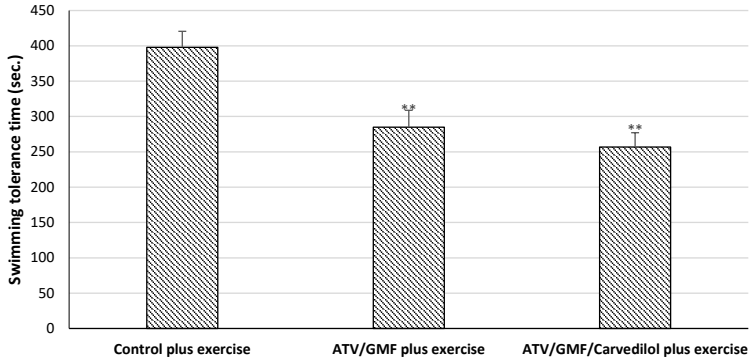

Figure 1. Swimming tolerance time of the rats in all groups

ATV: Atorvastatin (80 mg/kg/day for 10 days); GMF: Gemfibrozil (1000 mg/kg/day for 10 days); Carvedilol: 2.5 mg/kg/day for 10 days; Forced swimming was done on days 8, 9 and 10. Values are Mean±SEM (N=6). **P<0.01 compared with the control plus exercise group; One-way ANOVA followed by Tukey's post hoc test.

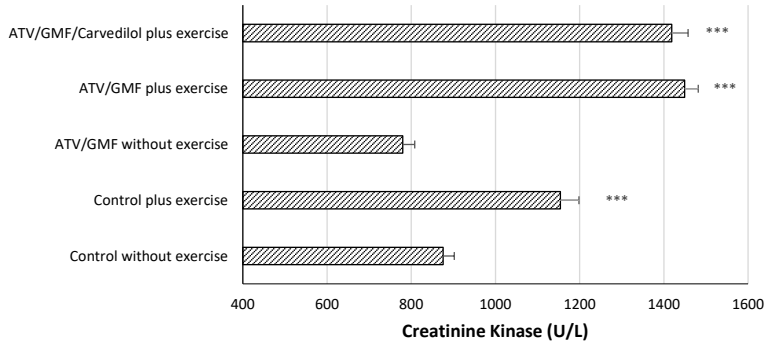

Figure 2. Plasma creatine kinase (CK) levels of rats in the control and treated groups

ATV: Atorvastatin (80 mg/kg/day for 10 days); GMF: Gemfibrozil (1000 mg/kg/day for 10 days); Carvedilol: 2.5 mg/kg/day for 10 days; Forced swimming was done on days 8, 9 and 10 as exercise. Values are Mean±SEM (n=6). ***P<0.001 in comparison with control group/groups; One-way ANOVA followed by Tukey post hoc test.

as seen in Figure 3, the LDH levels did not decrease significantly in groups 4 and 5 (P≤0.05).

Serum Aldolase: The means for serum aldolase levels in control Group 2 showed a significant rise compared to that for the control Group 1, where no exercise was performed (P<0.01). Likewise, the serum aldolase levels in the experimental Group 4, where exercise was performed, was significantly higher than those in both control Group 1 and experimental Group 3, where no exercise was done (P<0.01 & P<0.05, respectively). Also as seen in Figure 4, the means for serum aldolase levels in Groups 4 and 5, where exercise was performed, were not significantly different from each other (P≤0.05).

Discussion

Statin Drugs: A well known side effect of statin drugs is myopathy, which could worsen when taken together with a number of other drugs, such as macrolides [16] and fibrates [17]. The most severe form of rhabdomyolysis has been reported with the concurrent consumption of statins and fibrates [18]. Using statins at low dosages, if appropriate, with some fibrates, such as fenofibrate, minimizes the toxicity [18, 19]. Physical exercise may also aggravate statin-associated muscle damages, as manifested by elevated plasma levels of muscle-specific enzymes, especially CK [20]. The risk of myopathy is proportional to the degree of physical exertion, so that graded training programs provide time for adaptation of metabolic processes [21]. In the current study, we chose atorvastatin and gemfibrozil because of their frequent co-administration clinically. We also added unaccustomed intense physical activity to maximize the release of muscle enzymes from the injured rhabdomyocytes, and to test the possible role of carvedilol in the development of myopathy. Further, carvedilol was selected because it is

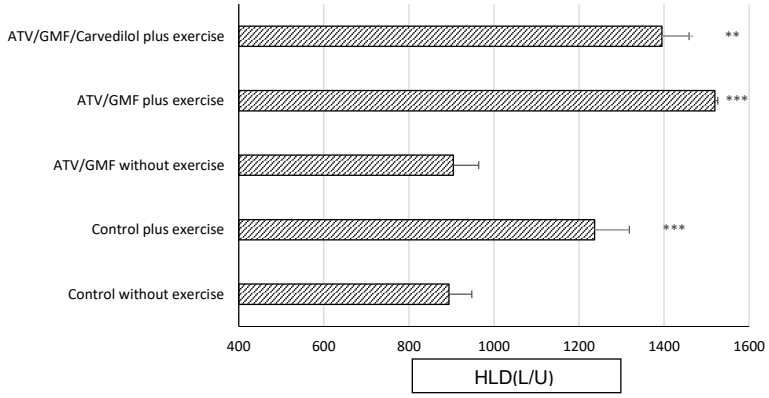

Figure 3. Plasma lactate dehydrogenase levels of the rats in all groups

ATV: Atorvastatin (80 mg/kg/day for 10 days); GMF: Gemfibrozil (1000 mg/kg/day for 10 days); Carvedilol: 2.5 mg/kg/day for 10 days; Forced swimming was done on days 8, 9 and 10. Values are Mean±SEM (n=6). ***P<0.001 compared with the controls; ** P< 0.01 compared with the control and exercise groups; One-way ANOVA followed by Tukey's post hoc test.

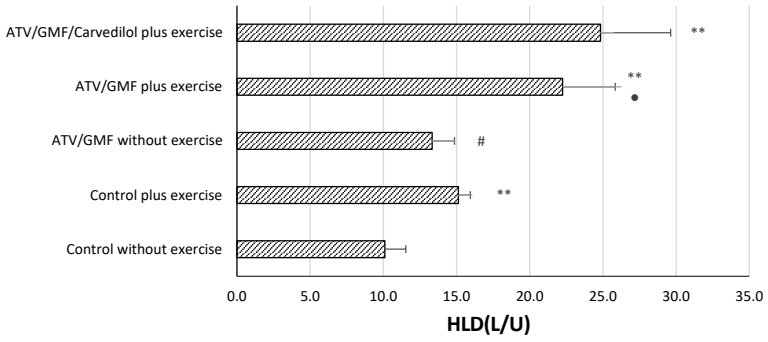

Figure 4. Aldolase levels of the rats' sera in the control and treatment groups

ATV: atorvastatin (80 mg/kg/day for 10 days); GMF: gemfibrozil (1000 mg/kg/day for 10 days); Carvedilol: 2.5 mg/kg/day for 10 days; Forced swimming was done in the days 8, 9 and 10 as exercise. Values are Mean±SEM (n=6). **P<0.01 in comparison with the control without exercise group; *P<0.05 in comparison with the ATV/GMF without exercise group; # P<0.05 in comparison with the control without exercise group; One-way ANOVA followed by Tukey's post hoc test.

commonly prescribed to patients suffering from cardiac ischemia, a well known side effect of hyperlipidemia and sedentary lifestyle.

Exercise effects: The impact of intense exercise and combined ATV and GMF was shown in this study by elevating the plasma levels of CK, aldolase and LDH in rats. Further, swimming tolerance time declined in rats that received ATV and GMF compared to those that received water only. Histopathological, electron microscopic and biochemical changes in striated muscles that were induced by statins, including the role of mitochondria in oxidative stress of such toxicities have already been described in rabbits and humans [3, 22]. Since histological examination of tissues is not practical in humans, we confined our study on just blood markers of muscle injury.

Carvedilol effects: The protective effects of carvedilol, as a β-2 receptor blocker, on oxidative stress and inflammation in muscle fibers have been addressed previously [13]. Carvedilol provides antioxidant protection against cardiac mitochondrial toxicity against doxorubicin [23]. Two studies have shown the effects of carvedilol on inflammation and oxidative stress in patients with chronic heart failure [24, 25]. This drug protects against the damages in the skeletal muscle myofibrils due to oxidation in patients with heart failure [14]. The thermogenic effect of carvedilol on the skeletal muscle in rats has been shown previously by microcalorimetry [26]. Carvedilol reduces skeletal muscle necrosis in ischemic states [27]. Further, β-adrenergic receptor agonists modulate skeletal muscle growth [28]. Catecholamines regulate local lactate production in vivo in skeletal muscles and adipose tissue via β-adrenergic receptors [29]. Consistent with the latter study, it has been found that β-adrenoceptor agonists are implicated in the force generation and intracellular calcium release in slow-twitch skeletal muscle fibers in rats [30].

Final remarks: In the current study, carvedilol did not significantly change the swimming tolerance time and the serum levels of the muscle-derived enzymes in rats after developing drug-induced myopathy. Whether the antioxidant effect of carvedilol or its β-2 adrenergic receptor blockade is more important in preserving muscle health requires well designed studies in the future.

Conclusions

Carvedilol does not significantly alter muscle enzyme levels or muscular activity tolerance in statin/fibrate-induced myopathy in rats. Despite the lack of ample evidence from humans, it could be assumed that carvedilol may be used safely in combination with lipid-lowering medications, pending future clinical safety studies in human subjects.

Ethical Considerations

Compliance with ethical guidelines

The animal care procedures were consistent with the guidelines set by the Ethics Committees at Shahid Sadoughi and Kerman Universities of Medical Sciences (Certificate #: Ir.ssu.Medicine.Rec.1398.237).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors were equally contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors wish to acknowledge the support of the management and staff of the Schools of Pharmacy at Shahid Sadoughi and Kerman Universities of Medical Sciences in Yazd and Kerman, respectively.

References

[1] Holder K. Myalgias and myopathies: Drug-induced myalgias and myopathies. FP Essent. 2016; 440:23-7. [PMID]

[2] Karr S. Epidemiology and management of hyperlipidemia. Am J Manag Care. 2017; 23(9 Suppl):S139-48. [PMID]

[3] Wen Z, Liang Y, Hao Y, Delavan b, Huang R, Mikailov M, et al. Drug-induced rhabdomyolysis atlas for idiosyncratic adverse drug reaction management. Drug Discov Today. 2019; 24(1):9-15. [DOI:10.1016/j.drudis.2018.06.006] [PMID] [PMCID]

[4] Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT et al. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. Am J Cardiol. 2010; 106(11):1594-601. [DOI:10.1016/j.amjcard.2010.07.041] [PMID]

[5] Jacobson TA. Myopathy with statin-fibrate combination therapy: Clinical considerations. Nat Rev Endocrinol. 2009; 5(9):507-18. [DOI:10.1038/nrendo.2009.151] [PMID]

[6] McClure DL, Valuck RJ, Glanz M, Murphy JR, Hokanson JE. Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population. J Clinical Epidemiology. 2007; 60(8):812-8. [DOI:10.1016/j.jclinepi.2006.11.006] [PMID]

[7] Elam MB, Majumdar G, Mozhui K, Gerling IC, Vera SR, Fish-Trotter H, et al. Patients experiencing statin-induced myalgia exhibit a unique program of skeletal muscle gene expression following statin re-challenge. PloS One. 2017; 12(8):e0181308. [DOI:10.1371/journal.pone.0181308] [PMID] [PMCID]

[8] Chatzizisis YS, Koskinas KC, Misirli G, Vaklavas C, Hatzitolios A, Giannoglou FD. Risk factors and drug interactions predisposing to statin-induced myopathy. Drug Saf. 2010; 33(3):171-87. [DOI:10.2165/11319380-000000000-00000] [PMID]

[9] Benveniste O, Musset L. Making the diagnosis of myositis: Laboratory testing in myositis. Managing Myositis: Springer; 2020; 161-6. [DOI:10.1007/978-3-030-15820-0_17]

[10] Accorsi A, Cramer ML, Girgenrath M. Fibrogenesis in LAMA2-related muscular dystrophy is a central tenet of disease etiology. Front Mol Neurosci. 2020; 13:3. [DOI:10.3389/fnmol.2020.00003] [PMID] [PMCID]

[11] Diogo CV, Deus CM, Lebiedzinska-Arciszewska M, Wojtala A, Wieckowski MR, Oliveira PJ. Carvedilol and antioxidant proteins in a type I diabetes animal model. Eur J Clin Invest. 2017; 47(1):19-29. [DOI:10.1111/eci.12696] [PMID]

[12] Soliman GF, Rashed LA, Morsi H, Ibrahim W, Abdollah H, Bastawy N, et al. Interrelation of liver vascularity to non-alcoholic fatty liver through a comparative study of the vasodilator effect of carvedilol or nicorandil in rats. Life Sci. 2019; 222:175-82. [DOI:10.1016/j.lfs.2019.02.057] [PMID]

[13] Dandona P, Ghanim H, Brooks DP. Antioxidant activity of carvedilol in cardiovascular disease. J Hypertens. 2007; 25(4):731-41. [DOI:10.1097/HJH.0b013e3280127948] [PMID]

[14] Dalla Libera L, Ravara B, Gobbo V, Danieli Betto D, Germinario E, Angelini A, et al. Skeletal muscle myofibrillar protein oxidation in heart failure and the protective effect of Carvedilol. J Mol Cell Cardiol. 2005; 38(5):803-7. [DOI:10.1016/j.yjmcc.2005.02.023] [PMID]

[15] Lucki I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behav Pharmacol. 1997; 8(6-7):523-32. [DOI:10.1097/00008877-199711000-00010] [PMID]

[16] Patel AM, Shariff S, Bailey DG, Juurlink DN, Gandhi S, Mamdani M, et al. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. Annals of Internal Medicine. 2013; 158(12):869-76. [DOI:10.7326/0003-4819-158-12-201306180-00004] [PMID]

[17] Blais JE, Tong GKY, Pathadka S, Chan EWY. Direct comparison of statins and fibrates on important efficacy and safety outcomes: systematic review and meta-analysis. Paper presented at: 12th Asian Conference on Pharmacoepidemiology (ACPE) and 25th Japanese Conference on Pharmacoepidemiology Joint Meeting. 11-13 October 2019; Kyoto, Japan. https://hub.hku.hk/handle/10722/279546

[18] Tournadre A. Statins, myalgia, and rhabdomyolysis. Joint Bone Spine. 2020; 87(1):37-42. [DOI:10.1016/j.jbspin.2019.01.018] [PMID]

[19] Ezad S, Cheema H, Collins N. Statin-induced rhabdomyolysis: A complication of a commonly overlooked drug interaction. Oxf Med Case Rep. 2018; 2018(3):omx104. [DOI:10.1093/omcr/omx104] [PMID] [PMCID]

[20] Bosomworth NJ. Statin therapy as primary prevention in exercising adults: Best evidence for avoiding myalgia. J Am Board Fam Med. 2016; 29(6):727-40. [DOI:10.3122/jabfm.2016.06.160085] [PMID]

[21] Berent T, Berent R, Steiner S, Sinzinger H. Statin-induced muscular side effects at rest and exercise-An anatomical mapping. Atheroscler Suppl. 2019; 40:73-8. [DOI:10.1016/j.atherosclerosissup.2019.08.026] [PMID]

[22] Nakahara K, Kuriyama M, Sonoda Y, Yoshidome H, Nakagawa H, Fujiyama J, et al. Myopathy induced by HMG-CoA reductase inhibitors in rabbits: A pathological, electrophysiological, and biochemical study. Toxicol Appl Pharmacol. 1998; 152(1):99-106. [DOI:10.1006/taap.1998.8491] [PMID]

[23] Oliveira PJ, Bjork JA, Santos MS, Leino RL, Froberg MK, Moreno AJ, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. Toxicol Appl Pharmacol. 2004; 200(2):159-68. [DOI:10.1016/j.taap.2004.04.005] [PMID]

[24] Toyoda S, Haruyama A, Inami S, Arikawa T, Saito F, Watanabe R, et al. Effects of carvedilol vs bisoprolol on inflammation and oxidative stress in patients with chronic heart failure. J Cardiol. 2020; 75(2):140-7. [DOI:10.1016/j.jjcc.2019.07.011] [PMID]

[25] Vescovo G, Ravara B, Danieli D, Angelini A, Dalla Libera L. Skeletal muscle protein oxidation in heart failure: The effect of carvedilol. J Mol Cell Cardiol. 2007; 42(6):147-55. [DOI:10.1016/j.yjmcc.2007.03.503]

[26] Fagher B, Monti M. Thermogenic effect of two β-adrenoceptor blocking drugs, propranolol and carvedilol, on skeletal muscle in rats. A microcalorimetric study. Thermochimica Acta. 1995; 251:183-9. [DOI:10.1016/0040-6031(94)02010-L]

[27] Hvaal K, Mathisen SR, Svindland A, Kirkeby OJ, Skjeldal S. Carvedilol reduces ischaemic skeletal muscle necrosis. J Orthop Res. 1999; 17(5):720-4. [DOI:10.1002/jor.1100170515] [PMID]

[28] Beermann DH. Beta-adrenergic receptor agonist modulation of skeletal muscle growth. J Anim Sci. 2002; 80(E-suppl-1):E18-23. https://academic.oup.com/jas/article-abstract/80/E-suppl_1/E18/4829614

[29] Qvisth V, Hagstrom-Toft E, Enoksson S, Bolinder J. Catecholamine regulation of local lactate production in vivo in skeletal muscle and adipose tissue: Role of β-adrenoreceptor subtypes. J Clin Endocrinol Metab. 2008; 93(1):240-6. [DOI:10.1210/jc.2007-1313] [PMID]

[30] Ha TNV. Effects of beta-adrenoreceptor drugs on force generation and intracellular calcium handling in slow-twitch skeletal muscle fibres of the rat. Muscle Nerve. 2004; 3(4):340-5. https://www.elibrary.ru/item.asp?id=5459495

This Page Intentionally Left Blank