IJBPAS, May, 2023, 12(5): 2094-2105

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

STATINS AND BEMPEDOIC ACID: A SYSTEMATIC REVIEW

SHARMA P[1*], KALRA A[1] AND UNIYAL S[2]

1: Master of Pharmacy (Pharmacology), Department of Pharmacology, "School of Pharmaceutical Sciences" "Shri Guru Ram Rai University", Patel Nagar, Dehradun, Uttarakhand, India

2: Assistant Professor, Department of Pharmacology, "School of Pharmaceutical Sciences", "Shri Guru Ram Rai University", Patel Nagar, Dehradun, Uttarakhand, India

***Corresponding Author: Pallavi Sharma: E Mail: psdell1006@gmail.com**

Received 5th July 2022; Revised 15th July 2022; Accepted 19th Sept. 2022; Available online 1st May 2023

https://doi.org/10.31032/IJBPAS/2023/12.5.7116

ABSTRACT

Cardiovascular disease [CVD] is the leading cause of death worldwide, and dyslipidemia is a key factor associated with an increased CVD risk. Although statin therapy is the first-line treatment for dyslipidemia, many sufferers do not attain their maximum capabilities low-density lipoprotein-cholesterol [LDL-C] levels even after taking moderate- or high-intensity statins; thus, non-statin therapy is frequently required. Bempedoic acid is a prodrug that, when activated, lowers LDL-C levels in the liver by inhibiting adenosine triphosphate citrate lyase. Bempedoic acid is approved by the FDA in 2020. On other hand Statins inhibitors of the hydroxymethyl glutaryl-CoA [HMG-CoA] reductase enzyme, are molecules of fungal origin. Statins are powerful cholesterol-lowering medications that operate by impeding a vital step in the sterol biosynthetic pathway. They have made contributions in prevention of CVD**.** Statins represent the cornerstone for the treatment of hypercholesterolemia, although muscle-related side effect are inevitable. This review is not a comparative but a descriptive analysis of Statins and Bempedoic acid.

Keywords: Hyperlipidemia; LDL-C; ACL, Adenosine triphosphate-citrate lyase; Dyslipidemia

INTRODUCTION

Hyperlipidemia refers to a group of inherited and acquired disorders associated with the high lipid levels in the body. It is a very common disorder, central and southwestern hemisphere, but also globally **[1]**. In the United States, cardiovascular disease is still the leading cause of morbidity and mortality **[2]**. Myocardial infarction, stroke, and

sudden cardiac death clinical manifestations **[3]**. Lessening plasma cholesterol levels has become essential to the study of preventive cardiology, and their use in both patients with coronary disease and healthy people has certainly contributed to the 50 percent reduction in coronary heart disease mortality in the United States over the last two decades **[4]**. The underlying cause of hyperlipidemia and atherosclerosis is complex, with multiple interacting genes at work **[5]**. These lipids are interconnected to blood plasma proteins and remain dissolved in the blood **[6]**. The key risk factors for hyperlipidemia are atherosclerosis, which sensitizes to ischemic heart disease and cerebrovascular disease **[7]**. A number of statistical trials have been conducted to investigate the impact of lipid-lowering medications on coronary heart disease [CHD] **[8]**. Further to that, because secondary causes can result in either an atherogenic lipoprotein profile with an increased risk of coronary heart disease [CHD] or severe hypertriglyceridemia with the chylomicronemia syndrome and an elevated chance of acute pancreatitis, defining the underlying secondary factors is vital in any clinical evaluation of lipids and lipoproteins **[9]**. The exact role of hyperlipidemia in lesion formation currently unexplained **[10]**. Inside some instances, specific lipid-lowering therapy may be required **[11]**. Almost all individuals benefit from dietary and exercise recommendations **[12]**. Bempedoic acid is a first-in-class low-density lipoprotein cholesterol [LDL-C] lowering agent which thus provides an important opportunity for increased LDL-C reduction in statin-intolerant patients or patients who require significant LDL-C reduction despite maximally tolerated statin therapy. Bempedoic acid, unlike statins, is administered as a prodrug and is converted to active form by a liver-specific enzyme. Bempedoic acid has the potential to reduce the risk of muscle-related adverse events, which can limit its use and effectiveness of statin therapy for the liver-specific mechanism of action **[13]**. By lowering LDL-C, statins have shown to decrease cardiovascular [CV] events in both primary and secondary prevention trials. For each mmol/L reduction in LDL-C, statins reduced major vascular events [myocardial infarction, coronary artery disease death, coronary revascularization, or stroke] by 22% over 5 years **[14, 15]**. The inhibition of HMG-CoA reductase may also result in pleiotropic effects, such as anti-inflammatory and antioxidant, although their clinical relevance remains unclear **[16]**.

STATINS

Statins inhibit the rate-limiting enzyme for de novo cholesterol synthesis in the mevalonate pathway, 3-hydroxy-3-methylglutaryl-Coenzyme A reductase [HMGCR] **(Figure 1)**. There are currently seven statins in the market: atorvastatin [ATV], fluvastatin [FVT], lovastatin [LVT], pitavastatin [PIT], pravastatin [PVT], rosuvastatin [RVT], and simvastatin [SVT] **[17]**. Statins have been associated with a multitude of beneficial pleiotropic effects, including anti-inflammatory, antioxidant, and immunomodulatory effects, platelet activation suppression, pyroptosis regulation, and enhanced plaque stability **[18–20]**.

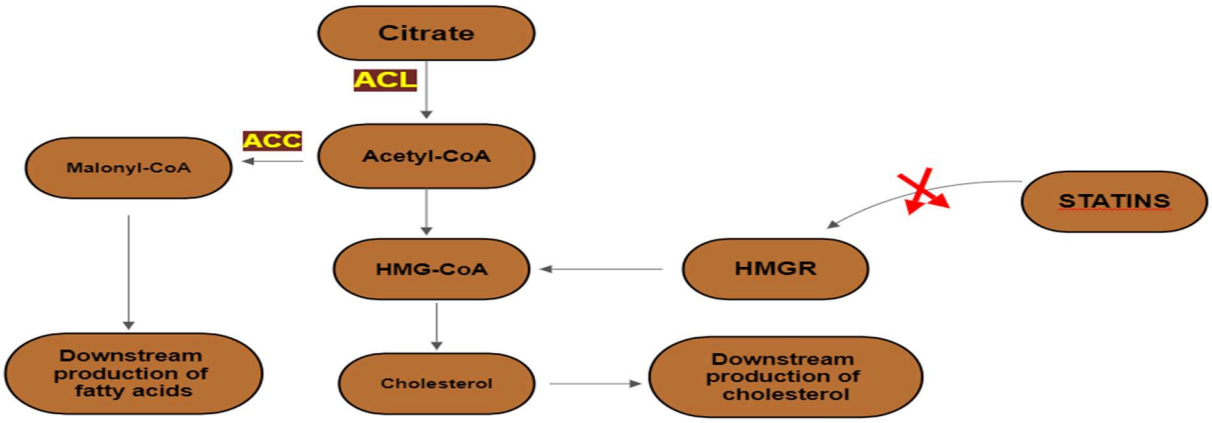

Figure 1: Statins inhibition of the mevalonate pathway
[*Abbreviations: ACL, Adenosine triphosphate-citrate lyase; ACC, acetyl-coA carboxylase; HMG-CoA, Hydroxy-methyl-glutaryl-coenzyme A; HMGR, Hydroxy-methyl-glutarylcoenzyme A reductase]

MECHANISM OF ACTION

Statins function by selectively blocking the formation HMG-CoA reductase, and hence restricting cholesterol biosynthesis and lowering hepatic cholesterol concentrations. These affect the expression of LDL-receptors [LDL-R] in liver cell membranes, which enhance clearance of circulating LDL-cholesterol particles from blood. Statin therapy brings down hepatic production rate of apo B100 comprising lipoproteins in specific patients, i.e. those with combined hyperlipidemia, ultimately leading to a reduction in both cholesterol and triglyceride concentrations **[21]**. Statins have recently been shown to enhance the expression of proprotein convertase subtilisin kexin type 9 [PCSK9], an enzyme responsible for LDL-R catabolism **[22]**. This may minimise the LDL-C lowering effect of statins **[23]** and their efficiency in CHD risk mitigation. Statin's hypocholesterolemic effect may be facilitated by a potential activity in reducing intestinal cholesterol absorption **[24]**. A

number of studies have found that statins have a changeable effect on high density lipoprotein [HDL] cholesterol levels **[25]**.

PHARMACOKINETICS

Following administration, all statins are rapidly absorbed, attaining peak plasma concentration [Tmax] within 4 hours **[26-29]**. The rate and extent of atorvastatin absorption is affected by time of day administration **[26]**, meanwhile the pharmacokinetic properties of rosuvastatin are unchanged **[30]**; nevertheless, the lipid-lowering effects of both drugs are similar whether given in the morning or evening **[26,30]**. This is constant with their long elimination half-lives in comparison to other approved statins, which have short elimination half-lives of 3 h or less **[27,28,31]** and are best administered in the evening, when the rate of endogenous cholesterol synthesis is maximum. Statins are chiefly metabolised by the cytochrome P450 [CYP450] enzyme family, which comprised of over 30 isoenzymes **[37]**. The principal active metabolites of atorvastatin are 2-hydroxy- and 4-hydroxy-atorvastatin acid **[38]**, meanwhile the major active metabolites of simvastatin are b-hydroxy acid and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives **[39,40]**. Fluvastatin is chiefly metabolised by the CYP2C9 isoenzyme, whereas pravastatin, pitavastatin, and rosuvastatin do not undergo significant CYP450 metabolism **[37, 41, 42]**. The majority of statins are eliminated chiefly through the bile after metabolism by the liver **[43]**.

ADVERSE EFFECT

1. **Possible diabetes**

   Statins are thought to boost insulin resistance in experimental animals **[44]**, however the mechanism underlying this onward effect is ambiguous. As a whole, clinical outcome studies show that statins raise the risk of diabetes by approximately 20–30% **[45]**.

2. **Liver toxicity**

   Pharmacovigilance studies with all statins have generally revealed a low incidence of severe liver toxicity. In studies with doses ranging from 10 to 40 mg of simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, and rosuvastatin, the incidence of elevated ALT > ULN ranged between 1% and 3% in the treatment groups versus 1.1 percent in the placebo group **[46]**. There was little evidence of severe liver toxicity in large scale incidence studies that included studies on liver patients **[47]**.

3. **Myopathy**

Severe rhabdomyolysis has been observed for over 20 years **[48]**. Large clinical trials do not typically indicate that this is a real issue: randomised clinical trials tend to enroll carefully selected patients, and myopathy is oftenly defined based on certain creatine-kinase [CK] threshold values. The true nature of muscle pain is oftenly unclear due to the lack of objective biochemical biomarkers. Since the percentage of patients with statin-induced myalgia have regular CK levels, a novel sensitive biomarker would be welcomed by both patients and physicians. A number of authors have related muscular side effects to lesser ubiquinone concentrations in serum and, as a consequence, muscle **[49]**, though the same authors have mentioned that ubiquinone reduction in serum does not result in lower levels in muscle after a short term statin therapies. The feasibility of ubiquinone administration in preventing muscle toxicity has remained a mystery **[50]**. Hanai *et al*. **[51]** describe a more straightforward mechanism of statin-induced muscle toxicity.

BEMPEDOIC ACID

Bempedoic acid [ETC-1002, 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid] is a novel lipid-regulating drug with a novel mechanism of action. It's a prodrug that gets transformed into bempedoic acid-CoA, that is a competitive inhibitor of the ACL enzyme. The liver preferentially helps to convert bempedoic acid to the active form [ETC-1002- CoA] **[52]**. ACL is the enzyme responsible for the hepatic production of cytosolic acetyl-coenzyme A, a precursor of the cholesterol biosynthesis mevalonate pathway. The major biochemical impact of bempedoic acid therapy is a rise in low-density lipoprotein-receptor activity and a consequent reduction in LDL-C plasma concentrations **[52]**.

MECHANISM OF ACTION

The major biochemical effects of bempedoic acid administration are a rise in LDL receptor activity and, as a consequence, a reduction in plasma LDL-C concentration **[52]**. Bempedoic acid is a prodrug of ETC-1002-coenzyme A [ETC-1002-CoA], that has LDL-C-lowering effect. ETC-1002-CoA prevents the enzyme ACL and inhibit the level of cytosolic acetyl-coenzyme A, a precursor of the mevalonate pathway of cholesterol biosynthesis **[53]**. ACL is a novel target for lowering LDL-C and CV risk

because it produces precursors for both fatty acid and cholesterol synthesis **[56]**. [Figure 2]. Bempedoic acid has been shown to be transformed into ETC-1002-CoA by hepatic acyl-CoA synthetase [ACS] **[52]**. In human liver subcellular fractions, ETC-1002-CoA formation coincides with ACSVL1 expression, and genetic silencing of ACSVL1 with small interfering RNAs has been shown to prevent bempedoic acid-CoA formation in McArdle cells. ACSVL1 is abundantly expressed in human liver microsomes, only moderately expressed in the kidney, and not found in skeletal muscle cells **[52]**. Thus, the circulation of ACSVL1 [and thus the sites of ETC-1002-CoA activity] appears to be ideal for disrupting hepatic cholesterol synthesis while having slight effect on other tissues **[52]**. The lack of ASCVL1 [and thus ETC-1002-CoA] in skeletal muscle, in particular, may allow for effective LDL-C lowering with a lower risk of muscle-related potential complications. These occurrences have been related to statin therapy and may be affected by the decline of mevalonate pathway products in skeletal muscle, which are downstream of HMG-CoA-reductase **[53-56]**.

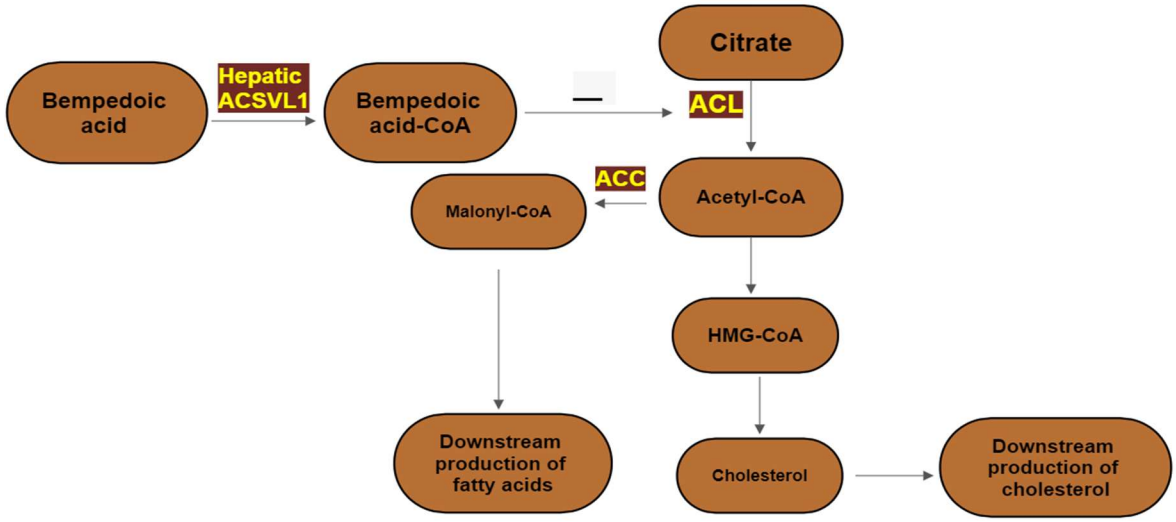

Figure 2: Bempedoic acid [ETC-1002] is converted to ETC-1002-CoA by ACSVL1. ETC-1002-CoA inhibits ACL and therefore reduces downstream production of cholesterol and fatty acids by the mevalonate pathway

PHARMACOKINETICS

Bempedoic acid is prescribed orally once daily due to a half-life generally range from 15 to 24 hours. It attains peak concentration in about 3.5 hours, and current research shows that concomitant food administration has no effect on oral bioavailability. A equivalent reaction was found with pravastatin, though the bempedoic acid dose in this case was 240 mg, which is not

currently available **[57]**. It is reversibly metabolised to another active metabolite, ESP15228. Both bempedoic acid(ETC-1002-CoA and ESP15228 are converted to inert glucuronide conjugates by UGT2B7. When compared to patients with normal renal function, the mean bempedoic acid area under the curve is higher in patients with renal impairment **[58]**.

ADVERSE EFFECT

According to data from Phase 3 clinical trials, bempedoic acid is well acceptable by the number of patients. In the pooled analysis of four Phase 3 trials, the most common adverse effects were nasopharyngitis [7%], urinary tract infection [4.5%], and arthralgia [4%] **[60]**. Due to a shortage of ACSVL1, it has been postulated that bempedoic acid may not interrupt the mevalonate pathway of cholesterol synthesis in skeletal muscle. As a consequence, a reduced incidence of myopathy is expected in comparison to statins **[61]**. As a whole muscle-related adverse effects, such as myalgia [5%], muscle spasm [3.7%], extremity pain [33%], and muscle weakness [0.5%], were disclosed in the bempedoic acid-treated group, though these events were similar to those reported in the placebo-treated group. Further to that, one of the chief causes for withdrawal of treatment in the bempedoic acid-treated groups was myopathy **[60]**. Moreover, tendon ruptures [0.2 percent] have been seen after bempedoic acid treatment, along with the Achilles tendon.

CONCLUSION

After more than 25 years of widespread use in primary and secondary cardiovascular prevention, and more than 40 years since their discovery, statins have provided both coronary benefit to millions of people and a large load of high-quality scientific data. Muscle pain and the influence on glucose metabolism are the most primary factors for statin discontinuation, non-adherence, and switching, which occurs at a rate of up to 75% within the first two years of treatment. Despite a slight reduction in LDL-C [20%], bempedoic acid has many advantages. Since bempedoic acid undergoes Phase 2 metabolism, it has a minimal risk of pharmacokinetic drug interactions. As a result, bempedoic acid emerges as a promising novel therapeutic agent for the treatment of dyslipidemia.

REFERENCES

[1] Hill MF, Bordoni B. Hyperlipidemia. [Updated 2022 Feb 8]. In: StatPearls [Internet]. Treasure Island [FL]: StatPearls Publishing; 2022 Jan

[2] Stewart, J., McCallin, T., Martinez, J., Chacko, S., & Yusuf, S. [2020].

Hyperlipidemia. *Pediatrics in Review*, *41*[8], 393-402.

[3] Eaton, C.B. [2005] Hyperlipidemia. *Primary Care: Clinics in Office Practice*, *32*[4], 1027-1055.

[4] Havel, R. J., & Rapaport, E. [1995]. Management of primary hyperlipidemia. *New England Journal of Medicine*, *332*[22], 1491-1498.

[5] Wouters, K, Shiri-Sverdlov, R., van Gorp, P. J., van Bilsen, M Hofker, M. H. [2005]. Understanding hyperlipidemia and atherosclerosis: lessons from genetically modified apoe and ldlr mice. *Clinical Chemistry and Laboratory Medicine [CCLM]*, *43*[5], 470-479.

[6] Harikumar, K. Ramunaik, M., & Suvarna, C. H. [2013]. A review on hyperlipidemic. *International journal of novel trends in pharmaceutical sciences*, *3*[4], 59-71.

[7] Asija R., & Charanjeet Singh, H. [2016] A comprehensive review on Antihyperlipidemic activity of various medicinal plants. *Int J Curr Pharm Rev Res*, *7*[6], 407-415.

[8] Walsh,J. M., & Pignone, M. [2004]. Drug treatment of hyperlipidemia in women. *Jama*, *291*[18], 2243-2252.

[9] Stone, N. J. [1994]. Secondary causes of hyperlipidemia. *Medical Clinics of North America*, *78*[1], 117-141.

[10] Ross, R. [1976].Harker. L Hyperlipidemia and atherosclerosis. *Science*, *193*, 1094.

[11] .Chait A., & Brunzell, J. D. [1990]. Acquired hyperlipidemia [secondary dyslipoproteinemias]. *Endocrinology and metabolism clinics of North America*, *19*[2], 259-278.

[12] Yu JN1,J A Cunningham, Thouin SR, Gurvich T, Liu D [2000],hyperlipidemia, europe pmc, pmid: 10918670

[13] Cicero AFG, Fogacci F, Cincione I. Evaluating pharmacokinetics of bempedoic acid in the treatment of hypercholesterolemia. Expert Opin Drug Metab Toxicol. 2021 Sep;17[9]:1031-1038. doi: 10.1080/17425255.2021.1951222. Epub 2021 Jul 15. PMID: 34197267.

[14] Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, *et al*. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376[9753]:1670–81.

[15] Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, *et al*. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular 26 Page 6 of 9 Curr Atheroscler Rep [2020] 22: 26 disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380[9841]:581–90.

[16] Ruscica M, Ferri N, Macchi C, Corsini A, Sirtori CR. Lipid lowering drugs and inflammatory changes: an impact on

cardiovascular outcomes? Ann Med. 2018;50[6]:461–84.

[17] Turner, R. M., & Pirmohamed, M. [2019]. Statin-related myotoxicity: a comprehensive review of pharmacokinetic, pharmacogenomic and muscle components. *Journal of clinical medicine*, *9*[1], 22.

[18] Kavalipati, N.; Shah, J.; Ramakrishan, A.; Vasnawala, H. Pleiotropic effects of statins. Indian J. Endocrinol. Metab. 2015, 19, 554–562.

[19] Wu, L.M.; Wu, S.G.; Chen, F.; Wu, Q.; Wu, C.M.; Kang, C.M.; He, X.; Zhang, R.Y.; Lu, Z.F.; Li, X.H.; *et al*. Atorvastatin inhibits pyroptosis through the lncrna nexn-as1/nexn pathway in human vascular endothelial cells. Atherosclerosis 2019, 293, 26–34.

[20] Gorabi, A.M.; Kiaie, N.; Hajighasemi, S.; Banach, M.; Penson, P.E.; Jamialahmadi, T.; Sahebkar, A. Statin-induced nitric oxide signaling: Mechanisms and therapeutic implications. J. Clin. Med. 2019, 8, 2051.

[21] Bilheimer DW, Grundy SM, Brown MS, Goldstein JL. Mevinolin and colestipol stimulate receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. Proc Natl Acad Sci U S A 1983;80:4124–8.

[22] Jeong HJ, Lee HS, Kim KS, Kim YK, Yoon D, Park SW. Sterol-dependent regulation of proprotein convertase subtilisin/kexin type 9 expression by sterol-regulatory element binding protein-2. J Lipid Res 2008;49:399–409.

[23] Huijgen R, Boekholdt SM, Arsenault BJ, Bao W, Davaine JM, Tabet F, *et al*. Plasma pcsk9 levels and clinical outcomes in the tnt [treating to new targets] trial: a nested case–control study. J Am Coll Cardiol 2012;59:1778–84.

[24] Miettinen TA, Gylling H. Cholesterol synthesis and absorption in coronary patients with lipid triad and isolated high ldl cholesterol in a 4s subgroup. Atherosclerosis 2003;168:343–9

[25] Ballantyne CM, Blazing MA, Hunninghake DB, Davidson MH, Yuan Z, DeLucca P, *et al*. Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: Results of the comparative hdl efficacy and safety study [CHESS].Am HeartJ 2003;146:862–9

[26] Cilla D.D. Jr, Gibson D.M., Whitfield L.R., Sedman A.J. Pharmacodynamic effects and pharmacokinetics of atorvastatin after administration to normocholesterolemic subjects in the morning and evening. J. Clin. Pharmacol. [1996] 36 604–609.

[27] Tse F.L., Jaffe J.M., Troendle A. Pharmacokinetics of fluvastatin after single and multiple doses in normal volunteers. J. Clin. Pharmacol. [1992] 32 630–638.

[28] Pan H.Y., DeVault A.R., Wang-Iverson D., Ivashkiv E., Swanson B.N., Sugerman A.A. Comparative pharmacokinetics and

pharmacodynamics of pravastatin and lovastatin. J. Clin. Pharmacol. [1990] 30 1128–1135.

[29] Warwick M.J., Dane A.L., Raza A., Schneck D.W. Single and multiple-dose pharmacokinetics and safety of the new HMGCoA reductase inhibitor ZD4522. Atherosclerosis [2000] 151 39

[30] Martin P.D., Mitchell P.D., Schneck D.W. Pharmacodynamic effects and pharmacokinetics of a new HMG-CoA reductase inhibitor, rosuvastatin, after morning or evening administration in healthy volunteers. Br. J. Clin. Pharmacol. [2002] 54 472–477

[31] Singhvi S.M., Pan H.Y., Morrison R.A., Willard D.A. Disposition of pravastatin sodium, a tissue-selective HMG-CoA reductase inhibitor, in healthy subjects. Br. J. Clin. Pharmacol. [1990] 29 239–243

[32] Naoumova R.P., Dunn S., Rallidis L. *et al*. Prolonged inhibition of cholesterol synthesis explains the efficacy of atorvastatin. J. Lipid Res. [1997] 38 1496–1500

[33] Yang B-B., Smithers J.A., Stern R.H. *et al*. Pharmacokinetics and dose proportionality of atorvastatin and its active metabolites. Pharm. Res. [1996] 13 [Suppl. 1] S43

[34] Kajinami K., Mabuchi H., Saito Y. NK-104: a novel synthetic HMG-CoA reductase inhibitor. Expert Opin. Investig. Drugs [2000] 9 2653–2661

[35] Garnett W.R. Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. Am. J. Health Syst. Pharm. [1995] 52 1639–1645

[36] Corsini A., Bellosta S., Baetta R., Fumagalli R., Paoletti R., Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol. Ther. [1999] 84 413–428

[37] Bottorff M., Hansten P. Long-term safety of hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors: the role of metabolism – monograph for physicians. Arch. Intern. Med. [2000] 160 2273–2280

[38] Jacobsen W., Kuhn B., Soldner A. *et al*. Lactonization is the critical first step in the disposition of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin. Drug Metab. Dispos. [2000] 28 1369–1378.

[39] Vickers S., Duncan C.A., Vyas K.P. *et al*. In vitro and in vivo biotransformation of simvastatin, an inhibitor of HMG CoA reductase. Drug Metab. Dispos. [1990] 18 476–483.

[40] Lennerna¨s H., Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Clin. Pharmacokinet. [1997] 32 403–425.

[41] Fujino H., Yamada I., Kojima J., Hirano M., Matsumoto H., Yoneda M. Studies on the metabolic fate of NK-104, a new inhibitor of HMG-CoA reductase [5]: in vitro metabolism and plasma protein binding in animals and human. Xeno. Metab. Disp. [1999] 14 415–424.

[42] McCormick A.D., McKillop D., Butters C.J. *et al*. ZD4522 – an HMG-CoA reductase inhibitor free of metabolically mediated drug interactions: metabolic studies in human in vitro systems. J. Clin. Pharmacol. [2000] 40 1055

[43] Knopp R.H. Drug treatment of lipid disorders. N. Engl. J. Med. [1999] 341 498–511

[44] Naples M, Federico LM, Xu E, Nelken J, Adeli K. Effect of rosuvastatin on insulin sensitivity in an animal model ofinsulin resistance: evidence for statin-induced hepatic insulin sensitization. Atherosclerosis 2008;198:94–103.

[45] Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. BMJ 2013;346:f2610.

[46] Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:52C–60C.

[47] Alqahtani SA, Sanchez W. Statins are safe for the treatment of hypercholesterolemia in patients with chronic liver disease. Gastroenterology 2008;135:702–4

[48] Corpier CL, Jones PH, Suki WN, Lederer ED, Quinones MA, Schmidt SW, *et al*. Rhabdomyolysis and renal injury with lovastatin use. Report of two cases in cardiac transplant recipients. JAMA: J Am Med Assoc 1988;260: 239–41.

[49] Sirtori CR, Mombelli G, Triolo M, Laaksonen R. Clinical response to statins: mechanism[s] of variable activity and adverse effects. Ann Med 2012;44:419–32.

[50] Mas E, Mori TA. Coenzyme Q[10] and statin myalgia: what is the evidence. Curr Atheroscler Rep 2010;12:407–13.

[51] Hanai J, Cao P, Tanksale P, Imamura S, Koshimizu E, Zhao J, *et al*. The musclespecific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. J Clin Invest 2007;117:3940–51.

[52] Pinkosky SL, Newton RS, Birch CM, *et al*. Abstract 17608: identification of a tissue-specific very long-chain Acyl-CoA synthetase involved in the inhibition of ATP-Citrate Lyase [ACL] by ETC-1002: a novel mechanism for cholesterol biosynthesis inhibition in the liver. Circulation. 2015;132:A17608.

[53] Parker BA, Gregory SM, Lorson L, *et al*. A randomized trial of coenzyme Q10 in patients with statin myopathy: rationale and study design. J Clin Lipidol. 2013;7:187–193.

[54] Lawrence J, Moyer C, Ameri M, *et al*. Abstract 13907: statin-induced myopathy is mediated by isoprenoid depletion and is independent of serum cholesterol levels. Circulation. 2014;130:A13907.

[55] Gluba-Brzozka A, Franczyk B, Toth PP, *et al*. Molecular mechanisms of statin intolerance. Arch Med Sci. 2016;12:645–658.

[56] Muntean DM, Thompson PD, Catapano AL, *et al*. Statin-associated myopathy and the quest for biomarkers: can we effectively predict statin-associated muscle symptoms? Drug Discovery Today. 2016; in press

[57] : Huyen Nguyen, Ikenna Akamnonu & Tianrui Yang [2021]: Bempedoic Acid: a cholesterol lowering agent with a novel mechanism of action, Expert Review of Clinical Pharmacology

[58] Nexletol. Package insert. Esperion Therapeutics, Inc; 2020. Revised February 2020. Accessed April 11, 2020.

[59] Nguyen, D., Du, N., Sulaica, E. M., & Wanat, M. A. [2021]. Bempedoic acid: a new drug for an old problem. *Annals of Pharmacotherapy*, *55*[2], 246-251.

[60] Bays HE, Banach M, Catapano AL, Duell PB, Gotto AM Jr, Laufs U, *et al*. Bempedoic acid safety analysis: pooled data from four phase 3 clinical trials. J Clin Lipidol. 2020;14[5]:649-59 e6.

[61] Pinkosky SL, Filippov S, Srivastava RA, Hanselman JC, Bradshaw CD, Hurley TR, *et al*. AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC1002, a novel small molecule regulator of lipid and carbohydrate metabolism. J Lipid Res. 2013;54[1]:134–51.