UNIVERISTY OF SANTO TOMAS
FACULTY OF PHARMACY
DEPARTMENT OF BIOCHEMISTRY

A COMPARATIVE STUDY OF SAFETY AND PHARMACOKINETIC PARAMETERS BETWEEN STATINS, BILE ACID SEQUESTRANTS, AND EZETIMIBE AS DIFFERENT CLASSES OF LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL-LOWERING DRUGS IN SILICO

Bulaon, Paul Armand C., Dimaculangan, Raine Alexandra O., Manalaysay, Xindrylle Anne C., Villanueva, Vincent E., Labrador, Alexis.

INTRODUCTION

CHOLESTEROL

- A lipophilic sterol constituent of bile salt used in digestion to facilitate absorption of fat-soluble vitamins.
- A nonpolar substance that is transported through the blood inside lipoproteins
- (Cox, R. A. et a., 2000):
  - Chylomicrons
  - Very-low-density lipoproteins (VLDL),
  - Intermediate-density lipoproteins (IDL)
  - High-density lipoproteins (HDL).
  - **Low-density lipoproteins (LDL)**

INTRODUCTION

ATHEROSCLEROSIS

- A disorder caused by excess cholesterol (LDL-cholesterol) in the blood which leads to the accumulation of fatty acids in the walls of the coronary arteries. (Asuka, E., 2021)

- As cholesterol builds up, atherosclerotic plaques form, narrowing and hardening the arterial walls (Lusis, A. J., 2000)

- These plaques can block the arteries and limit the amount of oxygen-rich blood that can reach the heart.

INTRODUCTION

LDL-CHOLESTEROL LOWERING DRUGS

- Statins (HMG-CoA reductase inhibitors)
- Ezetimibe (cholesterol absorbing inhibitors)
- Bile acid sequestrants (resins)

INTRODUCTION

STATINS

- Blocks the enzyme called HMG-CoA reductase in the synthesis mevalonate, a naturally occurring pathway that controls cholesterol production (Fookes, C., 2018).

- The primary line of drugs for treating lipid disorders and most effective at lowering LDL-C levels (Fookes, C., 2018).

- Also effective in lowering triglyceride levels in individuals with hypertriglyceridemia (Fookes, C., 2018).

- Doubling a dose of a statin will result in an approximately 6% reduction in LDL-C levels (Feingold, K. R., 2021).

INTRODUCTION

EZETEMIBE

- Prevents the absorption of cholesterol in an individual's intestine (U.S. National Library of Medicine, 2020).
- Used as a monotherapy to lessen the LDL-C levels of patients with statin intolerance (Feingold, K. R., 2021).
- Can also be used together with statin therapy if statin therapy alone does not work in lowering the LDL-C levels adequately (Feingold, K. R., 2021)..

INTRODUCTION

BILE ACID SEQUESTRANTS

- Binds with bile acids that contain cholesterol in the intestine and prevents reabsorption in the body (Sruthi M., 2021).
- Promotes apoprotein A1 synthesis which increases HDL-C (good cholesterol) levels
- Combining bile acids with statins and ezetimibe helps patients with Heterozygous familial hypercholesterolemia to lower down their LDL-C levels by 18% (Feingold, K. R., 2021).

INTRODUCTION

PHARMACOKINETICS

The study of how the body of an organism does to a certain drug when it enters, though, and leaves out of the body in terms of ADMET (Le, J., 2020).

- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicity

INTRODUCTION

STATEMENT OF THE PROBLEM

This study aimed to investigate the differences in terms of safety and pharmacokinetic parameters between Statins, Bile Acid Sequestrants, and Ezetimibe as different classes of Low-density Lipoprotein (LDL) cholesterol-lowering drugs in silico.

- What is the socio-demographic profile to assess the effectiveness of each drug?
- What are the impact risk factors and side effects of each LDL cholesterol drug?
- What is the connection between Statins, Bile Acid Sequestrants, and Ezetimibe in terms of LDL lowering cholesterol?
- How does the efficacy of LDL lowering cholesterol affect the safety and pharmacokinetics of Statins, Bile Acid Sequestrants, and Ezetimibe?

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INTRODUCTION

OBJECTIVES AND SIGNIFICANCE OF THE STUDY

General Objective:
Differentiate the three distinct types of drugs in each class of LDL cholesterol-lowering drugs in silico in terms of their safeness and pharmacokinetic parameters

Specific Objectives:

- Evaluate drug effectiveness based on socio-demographic factors and assess the impact of risk factors and side effects to determine the practical efficiency of LDL cholesterol-lowering drugs.

- Analyze drug correlations and pharmacokinetics related to immune response to avoid misuse, minimize side effects and comorbidities, and prevent new disease diagnoses

METHODOLOGY

ADMET

- It describes the **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion, and **T**oxicity. There are several ways to use ADMET, one of which is the in-silico ADMET.
- In silico ADMET tools distinguished and predicted the pharmacokinetic parameters of each LDL-cholesterol-lowering drug.

  - **Way2Drug - adverse drug effects and side effects.**
  - **SwissADME** - molecular structure and properties of the drugs.
  - **SwissTargetPrediction** - target classes of the drugs.
  - **ADMETlab 2.0** - drug warnings.

METHODOLOGY

SWISSADME

It utizilizes the BOILED-Egg method for interpreting results. It predicts two vital ADME parameters: passive gastrointestinal absorption (HIA) and brain access (BBB).

SWISSTARGETPREDICTION

This tool focuses on the target molecule of each specific drug and its distribution of the targeted drug molecule.

ADMETLAB 2.0

An enhanced AdmetLab tool that offers new and improved features such as systematic ADMET tool assessment, medicinal chemistry suitability, physicochemical properties, and early-stage toxicity evaluation of chemicals

WAY2DRUG PASS

It is an online drug that focuses on predicting the bioactivty specifically for ADMET properties.

METHODOLOGY

- SWISSADME
- SWISSTARGETPREDICTION
- ADMETLAB 2.0
- WAY2DRUG PASS

The key tool of this research, which were the ADMET tools, helped the researchers to achieve their aims and objectives due to each ADMET’s unique features.

RESULTS

STATINS

Physicochemical Properties	
Formula	C22H28FN3O6S
Molecular weight	481.54 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	12
Fraction Csp3	0.41
Num. rotatable bonds	10
Num. H-bond acceptors	9
Num. H-bond donors	3
Molar Refractivity	123.40
TPSA	149.30 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.40
Log $P_{o/w}$ (XLOGP3)	1.64
Log $P_{o/w}$ (WLOGP)	3.79
Log $P_{o/w}$ (MLOGP)	0.94
Log $P_{o/w}$ (SILICOS-IT)	2.54
Consensus Log $P_{o/w}$	2.26
Water Solubility	
Log *S* (ESOL)	-3.47
Solubility	1.64e-01 mg/ml ; 3.41e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.39
Solubility	1.97e-02 mg/ml ; 4.09e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-4.37
Solubility	2.05e-02 mg/ml ; 4.26e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.07 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MW>480
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	Yes
Bioavailability Score	0.56
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	4.60

Figure 1. Drug properties of Rosuvastatin taken from SwissADME

Physicochemical Properties	
Formula	C33H35FN2O5
Molecular weight	558.64 g/mol
Num. heavy atoms	41
Num. arom. heavy atoms	23
Fraction Csp3	0.27
Num. rotatable bonds	13
Num. H-bond acceptors	6
Num. H-bond donors	4
Molar Refractivity	158.26
TPSA	111.79 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.81
Log $P_{o/w}$ (XLOGP3)	4.96
Log $P_{o/w}$ (WLOGP)	6.54
Log $P_{o/w}$ (MLOGP)	3.48
Log $P_{o/w}$ (SILICOS-IT)	6.15
Consensus Log $P_{o/w}$	4.99
Water Solubility	
Log *S* (ESOL)	-5.99
Solubility	5.78e-04 mg/ml ; 1.03e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.05
Solubility	5.03e-05 mg/ml ; 9.00e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.13
Solubility	4.17e-07 mg/ml ; 7.46e-10 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.19 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 4 violations: MW>480, WLOGP>5.6, MR>130, #atoms>70
Veber	No; 1 violation: Rotors>10
Egan	No; 1 violation: WLOGP>5.88
Muegge	Yes
Bioavailability Score	0.56
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	4.95

Figure 2. Drug properties of Atorvastatin taken from SwissADME

Physicochemical Properties	
Formula	C25H38O5
Molecular weight	418.57 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	0
Fraction Csp3	0.76
Num. rotatable bonds	7
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	118.47
TPSA	72.83 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.84
Log $P_{o/w}$ (XLOGP3)	4.68
Log $P_{o/w}$ (WLOGP)	4.59
Log $P_{o/w}$ (MLOGP)	3.77
Log $P_{o/w}$ (SILICOS-IT)	3.77
Consensus Log $P_{o/w}$	4.13
Water Solubility	
Log *S* (ESOL)	-4.92
Solubility	5.01e-03 mg/ml ; 1.20e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.94
Solubility	4.84e-04 mg/ml ; 1.16e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-3.56
Solubility	1.15e-01 mg/ml ; 2.74e-04 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.53 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: more_than_2_esters
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	5.80

Figure 3. Drug properties of Simvastatin taken from SwissADME

RESULTS

BILE ACID SEQUESTRANTS

Physicochemical Properties	
Formula	C21H30ClN
Molecular weight	331.92 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	12
Fraction Csp3	0.43
Num. rotatable bonds	6
Num. H-bond acceptors	1
Num. H-bond donors	0
Molar Refractivity	105.33
TPSA	0.00 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	-2.34
Log $P_{o/w}$ (XLOGP3)	6.52
Log $P_{o/w}$ (WLOGP)	2.19
Log $P_{o/w}$ (MLOGP)	1.81
Log $P_{o/w}$ (SILICOS-IT)	5.42
Consensus Log $P_{o/w}$	2.72
Water Solubility	
Log *S* (ESOL)	-6.00
Solubility	3.35e-04 mg/ml ; 1.01e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.32
Solubility	1.60e-04 mg/ml ; 4.82e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.16
Solubility	2.30e-06 mg/ml ; 6.93e-09 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.70 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 2 violations: XLOGP3>5, Heteroatoms<2
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: anil_di_alk_E
Brenk	1 alert: quaternary_nitrogen_2
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	2.56

Figure 4. Drug properties of Cholestyramine taken from SwissADME

Physicochemical Properties	
Formula	C11H28ClN5O
Molecular weight	281.83 g/mol
Num. heavy atoms	18
Num. arom. heavy atoms	0
Fraction Csp3	1.00
Num. rotatable bonds	11
Num. H-bond acceptors	6
Num. H-bond donors	5
Molar Refractivity	74.69
TPSA	100.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.25
Log $P_{o/w}$ (XLOGP3)	-2.49
Log $P_{o/w}$ (WLOGP)	-1.70
Log $P_{o/w}$ (MLOGP)	-1.28
Log $P_{o/w}$ (SILICOS-IT)	-0.94
Consensus Log $P_{o/w}$	-0.63
Water Solubility	
Log *S* (ESOL)	0.71
Solubility	1.44e+03 mg/ml ; 5.10e+00 mol/l
Class	Highly soluble
Log *S* (Ali)	0.92
Solubility	2.34e+03 mg/ml ; 8.29e+00 mol/l
Class	Highly soluble
Log *S* (SILICOS-IT)	-2.56
Solubility	7.80e-01 mg/ml ; 2.77e-03 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-9.79 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: WLOGP<-0.4
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	No; 1 violation: XLOGP3<-2
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: Three-membered_heterocycle, alkyl_halide
Leadlikeness	No; 1 violation: Rotors>7
Synthetic accessibility	3.03

Figure 5. Drug properties of Colestipol taken from SwissADME

Physicochemical Properties	
Formula	C31H67Cl3N4O
Molecular weight	618.25 g/mol
Num. heavy atoms	39
Num. arom. heavy atoms	0
Fraction Csp3	0.81
Num. rotatable bonds	22
Num. H-bond acceptors	4
Num. H-bond donors	3
Molar Refractivity	183.32
TPSA	62.61 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	0.00
Log $P_{o/w}$ (XLOGP3)	8.90
Log $P_{o/w}$ (WLOGP)	4.49
Log $P_{o/w}$ (MLOGP)	0.30
Log $P_{o/w}$ (SILICOS-IT)	2.22
Consensus Log $P_{o/w}$	3.18
Water Solubility	
Log *S* (ESOL)	-7.83
Solubility	9.18e-06 mg/ml ; 1.49e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-10.10
Solubility	4.89e-08 mg/ml ; 7.92e-11 mol/l
Class	Insoluble
Log *S* (SILICOS-IT)	-4.43
Solubility	2.28e-02 mg/ml ; 3.69e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.75 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	No; 3 violations: MW>600, XLOGP3>5, Rotors>15
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	4 alerts: Three-membered_heterocycle, alkyl_halide, isolated_alkene, quaternary_nitrogen_2
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	5.35

Figure 6. Drug properties of Colesevelam taken from SwissADME

RESULTS

EZETIMIBE

Physicochemical Properties	
Formula	C24H21F2NO3
Molecular weight	409.43 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	18
Fraction Csp3	0.21
Num. rotatable bonds	6
Num. H-bond acceptors	5
Num. H-bond donors	2
Molar Refractivity	112.97
TPSA	60.77 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.51
Log $P_{o/w}$ (XLOGP3)	3.96
Log $P_{o/w}$ (WLOGP)	4.70
Log $P_{o/w}$ (MLOGP)	4.76
Log $P_{o/w}$ (SILICOS-IT)	4.72
Consensus Log $P_{o/w}$	4.33
Water Solubility	
Log *S* (ESOL)	-4.92
Solubility	4.91e-03 mg/ml ; 1.20e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.94
Solubility	4.74e-03 mg/ml ; 1.16e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.21
Solubility	2.55e-05 mg/ml ; 6.22e-08 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.99 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.37

Figure 7. Drug properties of Ezetrol and Zetia taken from SwissADME

Physicochemical Properties	
Formula	C19H36O5
Molecular weight	344.49 g/mol
Num. heavy atoms	24
Num. arom. heavy atoms	0
Fraction Csp3	0.89
Num. rotatable bonds	14
Num. H-bond acceptors	5
Num. H-bond donors	3
Molar Refractivity	97.63
TPSA	94.83 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.13
Log $P_{o/w}$ (XLOGP3)	4.77
Log $P_{o/w}$ (WLOGP)	4.47
Log $P_{o/w}$ (MLOGP)	3.05
Log $P_{o/w}$ (SILICOS-IT)	4.21
Consensus Log $P_{o/w}$	3.93
Water Solubility	
Log *S* (ESOL)	-4.06
Solubility	3.02e-02 mg/ml ; 8.77e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.49
Solubility	1.11e-04 mg/ml ; 3.22e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-3.76
Solubility	5.99e-02 mg/ml ; 1.74e-04 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.01 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	Yes
Bioavailability Score	0.56
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: Rotors>7, XLOGP3>3.5
Synthetic accessibility	2.69

Figure 8. Drug properties of Nexlizet taken from SwissADME

RESULTS

BOILED-EGG ILLUSTRATIONS

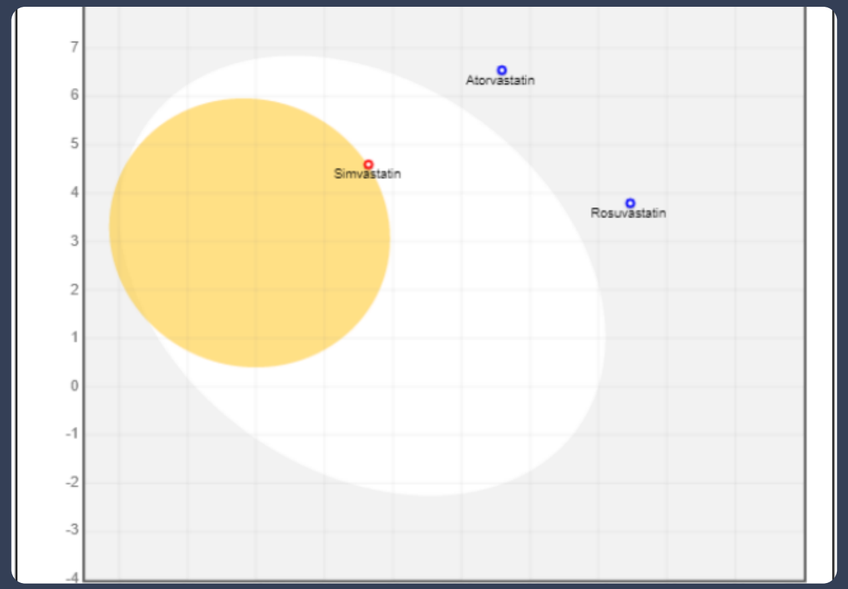

Figure 9. BOILED-Egg illustration of Statins

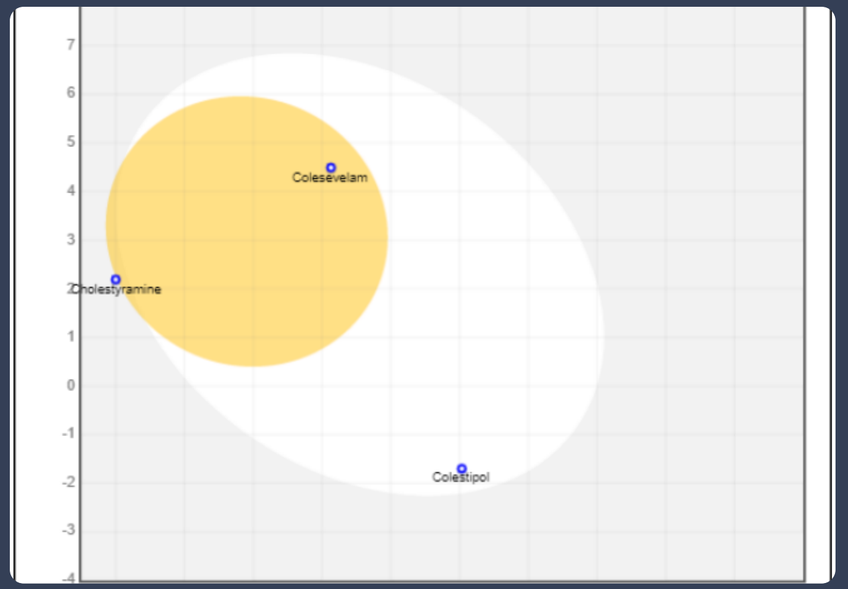

Figure 10. BOILED-Egg illustration of Bile Acid Sequestrants

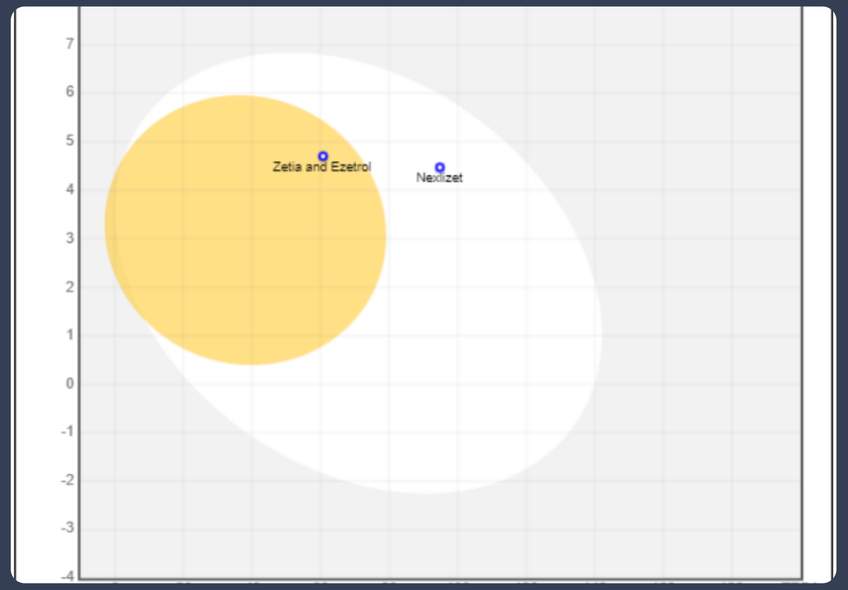

Figure 11. BOILED-Egg illustration of Nexlizet and Ezetrol/Zetia

RESULTS

ADVERSE REACTION

	Pa	Pi	Side Effect
Rosuvastatin	0.932	0.005	Nephrotoxicity
	0.509	0.191	Hepatotoxicity
Atorvastatin	0.980	0.006	Hepatotoxicity
	0.914	0.005	Nephrotoxicity
Simvastatin	0.981	0.003	Nephrotoxicity
	0.888	0.032	Hepatotoxicity

Figure 10. Adverse Reaction of Statins from Way2Drug ADVERPred

	Pa	Pi	Side Effect
Colestipol	0.562	0.031	Cardiac failure
	0.357	0.225	Arrhythmia
Colesevelam	0.402	0.104	Cardiac failure
	0.344	0.239	Arrhythmia

Figure 11. Adverse Reaction of Bile Acids Sequestrants from Way2Drug ADVERPred

	Pa	Pi	Side Effect
Nexlizet	0.745	0.015	Nephrotoxicity
	0.357	0.293	Hepatotoxicity

Figure 12. Adverse Reaction of Ezetimibe from Way2Drug ADVERPred

CONCLUSION

- Statin, bile acid sequestrant and ezetimibe are estimated to have a similar target age range between 60-76.
- The usage of these LDL-cholesterol lowering drugs showed equal effectiveness for both men and women.
- Bile acid sequestrants are best prescribed during pregnancy since they are not systemically absorbed as they bind with bile acids in the intestine.
- Ezetimibe is the best option for patients with comorbidities as they were observed to significantly reduce LDL-cholesterol production by 61%.

CONCLUSION

- Statins are the most commonly prescribed LDL-cholesterol drug by medical professionals as it is distinguished to simultaneously decrease LDL-C and increase HDL-C.

- Statins can also be co-administered with the two drugs such as ezetimibe, especially when under therapy to maximize their efficiency depending on the stage of severity and diagnosis.

- Bioavailability of statins may be decreased when taken with bile acid sequestrants.

RECOMMENDATIONS

- Have an initial medication prior to taking any Low-density Lipoprotein (LDL) cholesterol-lowering drugs to prevent adverse side effects if it is not suitable with the patient’s clinical situation.

- It is essential to follow all the precautions and warnings of the specific LDL-drugs before intaking considering the demographic profile of the patient.

- Future researchers should consider various kinds of drugs for future research to have a wider and diverse result in differentiating and identifying the relationship of different classes of Low-density Lipoprotein (LDL) cholesterol-lowering drugs in silico.

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