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)
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).
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?
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

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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 Absorption, Distribution, Metabolism, Excretion, and Toxicity. 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 utilizes 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 bioactivity specifically for ADMET properties.
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

Figure 1. Drug properties of Rosuvastatin taken from SwissADME

Figure 2. Drug properties of Atorvastatin taken from SwissADME

Figure 3. Drug properties of Simvastatin taken from SwissADME
RESULTS

BILE ACID SEQUESTRANTS

Figure 4. Drug properties of Cholestyramine taken from SwissADME

Figure 5. Drug properties of Colestipol taken from SwissADME

Figure 6. Drug properties of Colesevelam taken from SwissADME
# RESULTS

## EZETIMIBE

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

<table>
<thead>
<tr>
<th>Property</th>
<th>Ezetrol</th>
<th>Zetia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>338.5</td>
<td>471.5</td>
</tr>
<tr>
<td>Log P</td>
<td>-2.4</td>
<td>-2.7</td>
</tr>
<tr>
<td>Water solubility</td>
<td>0.2 mg/mL</td>
<td>0.1 mg/mL</td>
</tr>
<tr>
<td>CYP3A4 inhibition</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug class</td>
<td>HMG-CoA reductase inhibitor</td>
<td>HMG-CoA reductase inhibitor</td>
</tr>
</tbody>
</table>

### Figure 8. Drug properties of Nevilzot taken from SwissADME

<table>
<thead>
<tr>
<th>Property</th>
<th>Nevilzot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>338.5</td>
</tr>
<tr>
<td>Log P</td>
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</tr>
<tr>
<td>Drug class</td>
<td>HMG-CoA reductase inhibitor</td>
</tr>
</tbody>
</table>
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 Nexilzert and Ezetrol/Zetia
RESULTS

Figure 10. Adverse Reaction of Statins from Way2Drug ADVERPred

<table>
<thead>
<tr>
<th>Statin</th>
<th>Pa</th>
<th>Pi</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>0.952</td>
<td>0.005</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td>0.109</td>
<td>0.305</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0.992</td>
<td>0.003</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>0.814</td>
<td>0.186</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>0.981</td>
<td>0.003</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td>0.008</td>
<td>0.922</td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Sequestrant</th>
<th>Pa</th>
<th>Pi</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colestipol</td>
<td>0.942</td>
<td>0.001</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>0.357</td>
<td>0.295</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>0.802</td>
<td>0.104</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>0.844</td>
<td>0.256</td>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>

Figure 12. Adverse Reaction of Ezetimibe from Way2Drug ADVERPred

<table>
<thead>
<tr>
<th>Ezetimibe</th>
<th>Pa</th>
<th>Pi</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nexlizet</td>
<td>0.745</td>
<td>0.015</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td>0.357</td>
<td>0.293</td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>
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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REFERENCES


THANK YOU FOR LISTENING