



UNIVERSITI PUTRA MALAYSIA

***BENZIMIDAZOLE DERIVATIVES IN MANAGING CARDIOVASCULAR
DISEASE (CVD):
SYSTEMATIC REVIEW/
META-ANALYSIS***

NUR SHAFIRA MOHD SAYUTI

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ABSTRACT

Benzimidazole Derivatives in Managing Cardiovascular Disease (CVD): Systematic Review/Meta-Analysis

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Introduction: Cardiovascular disease (CVD) is the topmost leading cause of death worldwide. Previous studies reported that benzimidazole or its derivatives would be effective towards the cardiovascular disease by preventing blood clots and lowering high blood pressure. **Objective:** This study aims to analyse benzimidazole as anticoagulant or antihypertensive agents as well as to compare the effectiveness of benzimidazole (dabigatran, pimobendan, telmisartan and candesartan) with non-benzimidazole compound towards patients with cardiovascular conditions. **Methodology:** A systematic review was performed for studies related to benzimidazole and cardiovascular disease using five databases - PubMed, Scopus, Cochrane Library, Emerald Insight and Wiley Online Library. A total of 30 eligible studies were selected in this study. The risk of bias assessment either low or high was conducted to measure the risk of bias for each article. Lastly, all the extracted data were further analysed using meta-analysis to provide a summary result with the aid of forest plot. **Results:** With different cardiovascular condition, benzimidazole-derived compounds have demonstrated excellent potential as anticoagulant as well as antihypertensive agents. For anticoagulant, dabigatran works well as direct thrombin inhibitor in comparison to non-benzimidazole compounds such as warfarin, rivaroxaban and apixaban. Pimobendan acts as vasodilator in hypertensive patient, while telmisartan and candesartan function as angiotensin-receptor blocker (ARB). The outcome in the process of treating hypertension is good. **Discussion:** For oral anticoagulation, dabigatran may be considered as a first-line option. It has good efficacy and safety profile towards patients as compared to warfarin and rivaroxaban. It does not require routine anticoagulant monitoring. Warfarin is far less effective than dabigatran at preventing new thromboses in arteries in high-risk patients. For antihypertensive, pimobendan has been proven to be useful as an add-on treatment in patients with moderate-to-severe chronic heart failure who are on diuretic and digitalis medication, with or without vasodilator medication. It was well-tolerated and provided the maximal efficacy in acute and chronic heart failure patients. Telmisartan was well tolerated in patients with mild to moderate hypertension. With a half-life of roughly 24 hours, its activity lasts a long time in order to maintain blood pressure control during the once-daily dosage interval. Patient with mild to severe essential hypertension, oral candesartan cilexetil 8 to 32 mg given

once day decrease blood pressure dose-dependently. Candesartan was first discovered to be an effective once-daily antihypertensive therapy. **Conclusion:** In cardiovascular disease patients, dabigatran plays a significant role in preventing blood clotting as an anticoagulant. Meanwhile, pimobendan, telmisartan and candesartan are effective as antihypertensive agent in lowering high blood pressure.

Keywords: Cardiovascular disease (CVD), benzimidazole, anticoagulant, antihypertensive



ABSTRAK

Derivatif Benzimidazole dalam Merawat Penyakit Kardiovaskular: Kajian Sistematis / Analisis Meta

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Pengenalan: Penyakit kardiovaskular adalah penyebab kematian paling utama di seluruh dunia. Kajian sebelumnya melaporkan bahawa benzimidazole atau derivatifnya akan berkesan terhadap penyakit kardiovaskular dengan mencegah pembekuan darah dan menurunkan tekanan darah tinggi. **Objektif:** Kajian ini bertujuan untuk menganalisis benzimidazole sebagai agen antikoagulan atau antihipertensi serta membandingkan keberkesanan benzimidazole (dabigatran, pimobendan, telmisartan dan candesartan) dengan sebatian bukan benzimidazole terhadap pesakit. **Metodologi:** Kajian sistematik dilakukan untuk kajian yang berkaitan dengan penyakit benzimidazole dan kardiovaskular menggunakan lima pangkalan data - PubMed, Scopus, Perpustakaan Cochrane, Emerald Insight dan Perpustakaan Dalam Talian Wiley. Sebanyak 30 kajian yang layak dipilih dalam kajian ini. Risiko penilaian berat sebelah sama ada rendah atau tinggi dilakukan untuk mengukur risiko berat sebelah bagi setiap artikel. Terakhir, semua data yang diekstrak dianalisis lebih lanjut menggunakan meta-analisis untuk memberikan hasil ringkasan dengan bantuan plot hutan. **Keputusan:** Dengan keadaan kardiovaskular yang berbeza, sebatian yang berasal dari benzimidazole telah menunjukkan potensi yang sangat baik sebagai antikoagulan dan juga agen antihipertensi. Untuk antikoagulan, dabigatran berfungsi dengan baik sebagai perencat trombin langsung berbanding dengan sebatian bukan benzimidazole seperti warfarin, rivaroxaban dan apixaban. Pimobendan bertindak sebagai vasodilator pada pesakit hipertensi, sementara telmisartan dan candesartan berfungsi sebagai penyekat reseptor angiotensin. Hasil dalam proses merawat hipertensi adalah baik. **Perbincangan:** Untuk antikoagulasi oral, dabigatran boleh dianggap sebagai pilihan baris pertama. Ia mempunyai profil keberkesanan dan keselamatan yang baik terhadap pesakit berbanding dengan warfarin dan rivaroxaban. Ia tidak memerlukan pemantauan antikoagulan rutin. Warfarin jauh lebih berkesan daripada dabigatran dalam mencegah trombosis baru di arteri pada pesakit berisiko tinggi. Untuk antihipertensi, pimobendan terbukti berguna sebagai rawatan tambahan pada pesakit dengan kegagalan jantung kronik sederhana hingga teruk yang menggunakan ubat diuretik dan digitalis, dengan atau tanpa ubat vasodilator. Ia dapat diterima dengan baik dan memberikan keberkesanan maksimum pada pesakit kegagalan jantung akut dan kronik. Telmisartan dapat diterima dengan baik pada pesakit dengan

hipertensi ringan hingga sederhana. Dengan jangka hayat kira-kira 24 jam, aktiviti berlangsung lama untuk mengekalkan kawalan tekanan darah semasa selang dos sekali sehari. Pesakit dengan hipertensi penting ringan hingga teruk, candesartan cilexetil oral 8 hingga 32 mg diberikan sekali sehari mengurangkan tekanan darah bergantung kepada dos. Candesartan pertama kali ditemui sebagai terapi antihipertensi sekali sehari yang berkesan. **Kesimpulan:** Pada pesakit penyakit kardiovaskular, dabigatran memainkan peranan penting dalam mencegah pembekuan darah sebagai antikoagulan. Sementara itu, pimobendan, telmisartan dan candesartan berkesan sebagai agen antihipertensi dalam menurunkan tekanan darah tinggi.

Kata kunci: Penyakit kardiovaskular, benzimidazole, antikoagulan, antihipertensi

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LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
ACEI	Angiotensin-Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
ADP	Adenosine Diphosphate
AF	Atrial Fibrillation
AHF	Acute Heart Failure
AHFMR	Alberta Heritage Foundation for Medical Research
aPL	Antiphospholipid
APS	Antiphospholipid Syndrome
APTT	Activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
AT1	Angiotensin 1
B.I.D	Bis In Die (twice a day)
CA	Catheter Ablation
CAD	Coronary Artery Disease
CASE-J	Candesartan Antihypertensive Survival Evaluation in Japan
cGMP	Cyclic Guanosine Monophosphate
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval

CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM1	Diabetes Mellitus 1
DOAC	Direct Oral Anticoagulant
DTI	Direct Thrombin Inhibitor
DVT	Deep Vein Thrombosis
EC	Enzyme Commission
FDA	Food and Drug Administration
GP	Glycoprotein
GTP	Guanosine 5'-Triphosphate
HIT	Heparin-Induced Thrombocytopenia
I ²	Heterogeneity
IgA	Immunoglobulin A
IHD	Ischemic Heart Disease
INR	International Normalized Ratio
IUPAC	International Union of Pure and Applied Chemistry
JabRef	Java, Alver, Batada, Reference
MACE	Major Adverse Cardiac Event
MB	Major Bleeding
MI	Myocardial Infarction
NCD	Non-Communicable Disease
NCO	Net Clinical Outcome

NO	Nitric Oxide
NOAC	New Oral Anticoagulants
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulants
PAD	Peripheral Artery Disease
PAI	Platelet Aggregation Inhibitor
PDE	Phosphodiesterase
PE	Pulmonary Embolism
PICOS	Population, Intervention, Comparator, Outcome, Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RAAS	Renin–Angiotensin–Aldosterone System
RAS	Renin-Angiotensin System
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RF	Radiofrequency
SAR	Structure Activity Relationship
SBP	Systolic Blood Pressure
SE	Systemic Embolism
SPAF	Stroke Prevention in Atrial Fibrillation
STEMI	ST Elevation Myocardial Infarction
T80/H25	Telmisartan 80 mg/Hydrochlorothiazide 25 mg
TE	Thromboembolic

TEE	Transesophageal Echocardiogram
TF	Tissue Factor
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism



CHAPTER 1

INTRODUCTION

1.1 Background

Non-communicable diseases (NCDs) are the largest cause of mortality worldwide, killing 38 million people each year, with low- and middle-income countries accounting for over three-quarters of all deaths. Cardiovascular diseases (CVDs), malignancies, respiratory diseases, and diabetes are the four major NCDs (Al-Mawali, 2015). As a result, CVD would be the primary focus of research in this area. CVDs are the biggest cause of death worldwide, according to the World Health Organization (WHO) (2021), killing an estimated 17.9 million people each year. It is the leading cause of illness and mortality in the industrialised world, accounting for almost one-third of all deaths in the United States (US) (Abramov & Carson, 2012). CVDs are the leading cause of death worldwide, according to Al-Mawali (2015), with more people dying each year from CVDs than from any other cause. CVD has become a major contributor to worldwide mortality rates, and it is now the leading cause of death. Furthermore, heart attacks and strokes account for more than four out of every five CVD deaths, with one-third of these deaths occurring before the age of 70 (WHO, 2021).

From the term itself, CVDs are a condition related to heart and blood vessel. This condition is frequently intertwined with heart disease (Al-Mawali, 2015). From the same study, CVD includes coronary heart disease (CHD), congenital heart disease,

cerebrovascular illness, and other vascular disorders. Whereas, as stated by WHO, CVDs are comprised of coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other disorders. Coronary heart disease is defined as a condition that affects the blood arteries that supply the heart muscle. The blood arteries that supply the brain are then affected by cerebrovascular disease. Peripheral arterial disease, on the other hand, affects the blood arteries that feed the arms and legs. It is where rheumatic fever damages the heart muscle and heart valves, resulting in rheumatic heart disease. Streptococcal bacteria cause this infection. Next, congenital heart disease is another type of CVD that involves birth defects that disrupt the normal development and functioning of the heart due to anomalies of the heart anatomy. Finally, deep vein thrombosis and pulmonary embolism are also types of CVD in which blood clots in the veins of the legs. This problem can deteriorate to the point when it dislodges and travels to the heart and lungs.

Benzimidazole compounds have gained a lot of attention due to their positive characteristics, such as improved stability, bioavailability, significant biological activity and antihypertensive agent (Kamanna, 2019). Benzimidazoles are heterocyclic aromatic compounds with a structural property of a six-membered benzene moiety fused to a five-membered imidazole moiety (Gaba & Mohan, 2015). This chemical was chosen for research because it is believed to have a unique nucleus known as the "Master Key." This is widely considered to be an essential core in many compounds that act on various targets to produce a variety of pharmacological effects (Bansal & Silakari, 2012). As a result, the numerous benzimidazole-based compounds developed, synthesised, and assessed in the current review by Bansal and Silakari (2012) have been grouped based on their biological activities.

Anticoagulant, antihypertensive, anti-inflammatory, antibacterial, antifungal, anthelmintic, antiviral, antioxidant, antiulcer, anticancer, and many other activities are among the most common. In clinics, a variety of chemicals derived from the benzimidazole nucleus are used to treat a variety of disorders (Bansal & Silakari, 2012).

With that, benzimidazole nucleus has been thoroughly investigated as an antihypertensive agent for the creation of antihypertensive medicines (Bansal & Silakari, 2012). Antihypertensive drugs work through a variety of mechanisms, including vasodilators, angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme inhibitors (ACEIs). Many benzimidazole-based compounds, according to Bansal and Silakari (2012), serve as antihypertensives by interfering with the Renin–Angiotensin System (RAS). Moreover, various publications have been published highlighting the use of the benzimidazole nucleus in the synthesis of antihypertensive compounds. Blockade of the renin–angiotensin system (RAS) is a typical mechanism used by the majority of benzimidazole derivatives to demonstrate their antihypertensive potential. RAS is a complex physiological mechanism that controls vasoconstriction, resulting in hypertension (Singh & Silakari, 2018).

Anticoagulants, on the other hand, are other source of concern for people with cardiovascular disease. Anticoagulants are therefore in significant demand in today's medicine (Hu & Liu, 2020). Because thrombin is the ultimate effector in blood coagulation, it is a reasonable target for new anticoagulants (Hu & Liu, 2020). According to Bansal and

Silakari (2012), the benzimidazole nucleus acts as a good template for placing the various substituents essential for thrombin interaction. Furthermore, according to the study Bansal and Silakari (2012), Ueno et al. conducted structural activity relationship (SAR) experiments that led to benzimidazole derivatives being effective and selective factor Xa inhibitors with outstanding anticoagulant action and no fatal acute toxicity. In addition to the same study, another family of drugs for treating thromboembolic illnesses is the inhibitor of factor VIIa/Tissue Factor (fVIIa/TF) complex.

A few systematic reviews have described that benzimidazole are potentially drug compound alternative in CVD patients. For instance, dabigatran works as blood thinner that aid in the smooth passage of blood vessels. It helps to prevent blood clots from developing or growing in size. Hence, dabigatran is believed to treat certain types of heart disease as well as other conditions that could lead to blood clot formation (Iturbe-Hernandez et al., 2020). While pimobendan works as vasodilator in which to dilate the blood vessels. It has an effect on the muscles that lining inside of the arteries and veins, preventing them from tightening and narrowing. As a result, blood will flow more freely through the vessels and this will reduce high blood pressure (Kato, 1997). Whereas for telmisartan and candesartan cilexetil, they have the same role as pimobendan in which to reduce blood pressure. But, these two drugs have different mechanism as antihypertensives agents. They are known as angiotensin-receptor blocker (ARB). ARBs function by inhibiting the hormone's receptors, particularly angiotensin 1 (AT1) receptors that present in the heart and blood vessels. Blocking the activity of angiotensin II can lower the blood pressure and protect the heart from harm (Israili, 2000).

To summarize, benzimidazole is a heterocyclic aromatic chemical molecule that has long been recognized as a valuable pharmacophore and favored structure in medicinal chemistry. Substituted benzimidazoles are of great interest since they exhibit a broad range of biological action and are low in toxicity (Ates-Alagoz, 2016). As a result, a systematic review and meta-analysis are employed to analyze all existing findings of benzimidazole-derivatives compounds on their potential as anticoagulant and antihypertensive medicines in cardiovascular diseases. Hence, this paper aims to examine the effectiveness of benzimidazole compounds as anticoagulant and antihypertensive drugs for treatment of CVD patients. This study will also compare benzimidazole with compounds that are not derived from benzimidazole by meta-analysis.

1.2 Objectives

1.2.1 General Objective

This study generally aimed to study the effectiveness of benzimidazole drug compound on CVD patients as compared to non-benzimidazole compound.

1.2.2 Specific Objective

The specific objectives of this study are to use systematic review and meta-analysis to assess the efficacy of benzimidazole drug compounds in which (1) dabigatran as anticoagulant while (2) pimobendan, telmisartan and candesartan cilexetil as antihypertensive agents in managing cardiovascular conditions.

1.3 Hypothesis

It is hypothesized that systematic review and meta-analysis may reveal that benzimidazole compounds are efficient as anticoagulant and antihypertensive agents in treating patients with cardiovascular disease.

CHAPTER 2

LITERATURE REVIEW

2.1 Cardiovascular Disease

Cardiovascular diseases (CVD) are now a major public health concern around the world, with ischemic heart disease (IHD) or coronary heart disease (CHD) being the most frequent with the older population is being increasingly affected (Asif, n.d.). According to the same study by Olvera et al., (2021), coronary artery disease (CAD), also known as coronary heart disease (CHD), cerebrovascular disease (CVD), peripheral artery disease (PAD), and aortic atherosclerosis are all examples of cardiovascular illness (also known as heart disease). Coronary artery disease (CAD) is caused by a reduction in myocardial perfusion, which can lead to angina, myocardial infarction (MI), and/or heart failure. It is responsible for one-third to half of all CVD cases. While according to Asif (n.d.), coronary artery disease (CAD), either alone or in combination with hypertension, is the most common cause. Hypercholesterolemia, diabetes mellitus, obesity, and smoking may all increase the chance of developing this disease. On the other hand, stroke and transient ischemic attack (TIA) are examples of cerebrovascular disease. Whilst, peripheral artery disease (PAD) is a condition that affects the arteries in the legs. Particularly limb-related arterial disease, which can lead to claudication. Thoracic and abdominal aneurysms are part of aortic atherosclerosis (Olvera et al., 2021).

In terms of causality, CVD can be caused by a variety of factors, such as emboli in a patient with atrial fibrillation which resulting in ischemic stroke or rheumatic fever causing valvular heart disease. This addressing risk factors associated with the development of atherosclerosis is critical because it is a common denominator in the pathophysiology of CVD (Olvera et al., 2021). Whereas, in terms of morbidity and mortality, the worldwide burden of CVD is enormous. Annually, an estimated 128 million people are affected, mostly by non-fatal cardiovascular events and their long-term consequences; this number is expected to rise as the world's population ages and obesity and related cardiovascular risk factors, such as diabetes mellitus, hypertension, and hypercholesterolemia, become more prevalent (Frampton, 2011).

2.1.1 Mechanism of Anticoagulant

Coagulation is a complicated process in which blood clots to block and finally halt bleeding. It is considered as one of the most harmful processes in cardiovascular disease (Hu & Liu, 2020). It is a condition where a platelet and a fibrin-containing clot plug the bleeding. Deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction with ST elevation (STEMI), and ischemic stroke are all prevented by anticoagulants, which work to prevent blood coagulation (clotting). According to Hu & Liu (2020), anticoagulants are currently divided into two types of anticoagulation mechanisms: direct thrombin inhibitors (DTIs) and platelet aggregation inhibitors (PAIs).

Direct thrombin inhibitors (DTIs) are a new class of anticoagulants that bind to thrombin directly and prevent it from interacting with its substrates (Di Nisio et al., 2005). According to study by Lee and Ansell (2011), direct thrombin inhibitors (DTIs) bind to thrombin directly and do not require a cofactor like antithrombin to work. Both soluble and fibrin-bound thrombin are inhibited by DTIs. Other major benefits include a more predictable anticoagulant action compared to heparins, an anti-platelet impact, and the absence of immune-mediated thrombocytopenia. This study was also supported by Kaplan and Francis (2002) as they mentioned that direct thrombin inhibitors bind to thrombin and prevent it from catalysing a variety of substrates. In contrast to heparin and its derivatives, which inhibit thrombin and other coagulation serine proteases via antithrombin, and warfarin-type drugs, which interfere with the synthesis of the coagulation serine proteases' precursors, they inhibit thrombin and other coagulation serine proteases via antithrombin (Kaplan & Francis, 2002).

In this case, the major effector enzyme thrombin is responsible for the final stage in the thrombus formation process. Effective suppression of thrombin is critical in the prevention and treatment of thrombotic diseases because of its prominent role in thrombus creation, propagation, and stability. Inhibition of thrombin can be done in two ways: indirectly or directly. Anticoagulants like heparin (both unfractionated and fractionated) and vitamin K antagonists are indirect thrombin inhibitors. For the past five decades, indirect thrombin inhibitors have been the most commonly used anticoagulants in clinical practise. These classic anticoagulant medicines, while

effective when administered correctly, have a number of drawbacks (Nutescu et al., 2008). While the non-vitamin K antagonist oral anticoagulant dabigatran is a direct thrombin inhibitor (DTI) used to prevent stroke and systemic embolism in people with nonvalvular atrial fibrillation (Trabold et al., 2019).

Whereas in some studies, platelets have recently been discovered to be involved in all phases of atherosclerosis. The acute vascular closure at the site of atherosclerotic plaque rupture is a key platelet-mediated mechanism, and there is accumulating evidence for platelet adherence to endothelial cells in the early stages of atherosclerosis. This results in the formation of an atherosclerotic plaque as a result of the interaction of other cells. In study by Gomes and Verheugt (2003), they explained that platelet aggregation is a crucial factor in the progression of atherosclerosis problems. Complications like myocardial infarction and sudden death can be avoided by pharmacologically suppressing platelet aggregation.

In relation to that, platelet aggregation inhibitors (PAI) are one of the most commonly prescribed medications in the elderly, despite a paucity of information on the dangers and advantages of their use in this population (Ahrens et al., 2005). According to a systematic review by Meinshausen et al. (2017), PAI are among the most commonly recommended medications among adults over the age of 65. They are used to prevent cardiovascular disease, as well as before and after myocardial infarction or acute coronary syndrome, angioplasty and stenting, stroke and transient ischemic attacks (TIA), and peripheral artery occlusive disease prevention. The

suppression of thrombocyte activation and/or inhibiting aggregation is the pharmacological mechanism of action of PAI. The purpose of treatment is to avoid thrombotic consequences (Meinshausen et al., 2017).

Antiplatelet therapy is currently accessible in the form of orally and intravenously delivered medicines. Some of them work together to limit platelet adhesion and aggregation at distinct stages. Inhibition of cyclooxygenase, phosphodiesterase inhibition, blockade of the P2Y₁₂ adenosine diphosphate (ADP) receptor, and blockade of the glycoprotein (GP) IIb/IIIa receptor are currently clinically authorised techniques for platelet function inhibition (Ahrens et al., 2005). From study by Ahrens et al., (2005), antiplatelet therapy, in addition to dietary, cholesterol- and lipid-lowering, and other pharmaceutical treatments, is an important aspect of the treatment of atherosclerosis and its many clinical symptoms.

In all, anticoagulants are in high demand in today's medicine. For example, the prevalence of atrial fibrillation is expected to rise from 5.2 million cases in 2010 to 12.1 million cases in 2030 in the United States (Hu & Liu, 2020). In conjunction to that, Hu and Liu (2020), had mentioned in the study saying that thrombin is a platelet agonist with a high affinity for platelets. That is why thrombin is a reasonable target for novel anticoagulants because it is the ultimate effector in blood coagulation.

2.1.2 Mechanism of Antihypertensive

Hypertension is a substantial cardiovascular risk factor, not only because of its impact on vascular illness, but also because of its widespread occurrence in the community (Ross & Papademetriou, 2004). Hypertension is a major contributor to the development of cardiovascular disease. The angiotensin receptor blockers (ARBs) are generally successful at lowering blood pressure with few side effects, particularly cough and angioedema, which is their main advantage over angiotensin-converting enzyme (ACE) inhibitors (McFarlane, 2011). It is generally known that hypertension is a major cardiovascular risk factor (Foulquier et al., 2014). Although hypertension is a substantial cardiovascular risk factor, most people go undiagnosed for years (Ross & Papademetriou, 2004). Ideally, antihypertensive medication should keep blood pressure under control throughout the 24-hour dosing cycle, especially in the last 6 hours (McFarlane, 2011). There are several mechanisms of antihypertensive agents including, vasodilator, ARBs and ACE inhibitors.

Vasodilators are used to treat a range of illnesses, the most prevalent of which being systemic hypertension. Myocardial infarction (both ST-segment elevation and non-ST-segment elevation), angina, heart failure, stroke, chronic renal disease, preeclampsia, and hypertensive crises are only a few of the other disorders. Different kinds of vasodilators are employed in clinical practise today, and each has a unique effect on the coronary arteries and peripheral vasculature (arteries and veins). Vasodilators primarily impact the arteries in the human body, although some

vasodilators (such as nitroglycerin) can also affect the body's venous system (Hariri & Patel, 2021).

According to the same study by Hariri and Patel (2021), they explained that vasodilators dilate or prevent constriction of blood arteries, allowing more blood to circulate to the body's numerous organs. Many vasodilators attach to receptors on blood vessel endothelial cells, causing calcium release. The enzyme nitric oxide synthase (NO synthase) is activated by calcium, which converts L-arginine to NO. Diffusion allows it to escape the endothelial cell and enter vascular smooth muscle cells. GTP is activated by NO and converted to cGMP. The myosin-light chain phosphatase enzyme is then activated, removing a single phosphate from myosin and actin filaments. Vascular smooth muscle relaxes when myosin and actin filaments are dephosphorylated.

In conjunction to that, diuretics and vasodilators are crucial components of AHF pharmacologic therapy when fluid excess and congestion are present (Travessa & Menezes, 2018). Only a small percentage of patients with acute heart failure have cardiogenic shock; the majority have elevated left ventricular filling pressure and high or normal blood pressure. In this case, vasodilator therapy in the acute setting can help with both hemodynamics and symptoms (Hollenberg, 2007).

In study by Metra et al. (2008), vasodilators are suggested for the treatment of acute heart failure (AHF) that is accompanied by an increased blood pressure at

the time of presentation. It's because most research suggests that vasoconstriction plays a key role in the pathophysiology of AHF through a variety of mechanisms. However, we feel that vasodilators should be given to AHF patients with normal or high blood pressure (BP) when they first present. They should not be given to individuals with low blood pressure since they might cause hypotension and hypoperfusion of essential organs, which can lead to renal and/or cardiac damage, worsening the patient's condition.

Whereas, in patients with heart failure, a history of ST-elevation myocardial infarction, diabetes, or proteinuria, renin-angiotensin-aldosterone system blockers such as ACE inhibitors and ARBs are the first-line of treatment. Both classes of drugs have cardioprotective and renoprotective properties (Hariri & Patel, 2021). According to them, ACE inhibitors are used to suppress the conversion of angiotensin I to angiotensin II, a powerful vasoconstrictor. ARBs, on the other hand, are used to keep angiotensin II from attaching to its receptor. While Taylor et al., (2011) had mentioned in their study that ARBs bind to the angiotensin II AT1 receptor, which inhibits the cellular activities of angiotensin II mediated by the receptor in which the tissue is located, unlike ACE inhibitors, which prevent the conversion of angiotensin I to II.

In general, the renin–angiotensin–aldosterone system (RAAS) plays a key role in cardiovascular (CV) function throughout this continuum, and prolonged activation has negative pathophysiologic consequences. As a result, RAAS blocking

has emerged as a critical technique for reducing the negative consequences of RAAS activation and thereby improving CVD outcomes (Abramov & Carson, 2012). The RAAS is implicated in the pathophysiology of a number of disorders, including hypertension, congestive heart failure, and all types of chronic kidney disease, including diabetic nephropathy (Hill & Vaidya, 2021).

The emphasis on reducing overall cardiovascular risk and treating the underlying causes of cardiovascular disease has shifted with new approaches to the definition and treatment of hypertension. Activation of RAAS has emerged as a key element in the pathophysiology of endothelial dysfunction and cardiovascular disease over the last several decades (CVD). Although angiotensin-converting enzyme inhibitors (ACEIs) have been shown to be effective in the treatment of CVD, side effects such as cough and angioedema may limit their use. ARBs are a type of RAAS inhibitor that is regarded a potential alternative to ACEIs (Abramov & Carson, 2012).

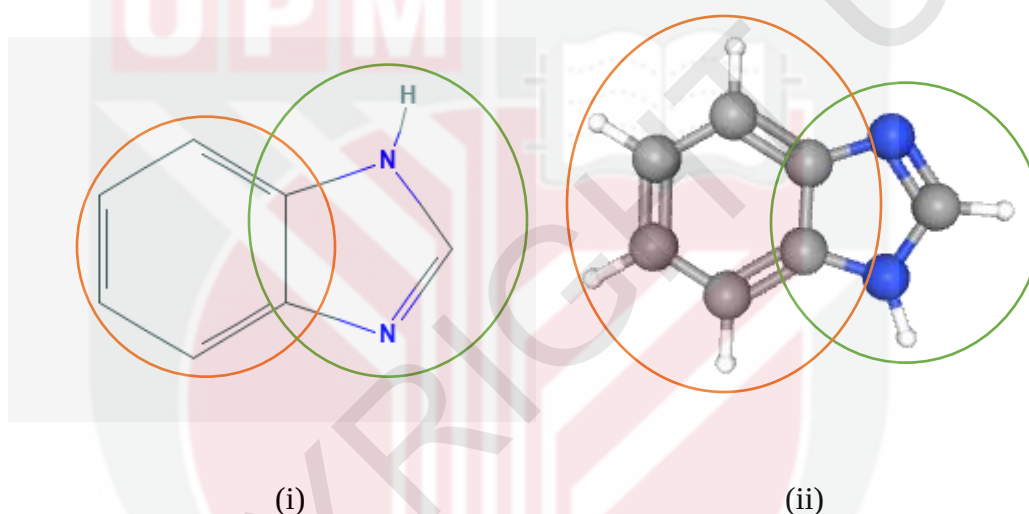
ARBs appear to be beneficial in improving CV outcomes, according to the existing evidence. Their effectiveness is most clearly demonstrated in congestive heart failure, with the greatest advantages evident in fewer hospitalizations (Abramov & Carson, 2012). Whilst, ACEIs are extremely effective antihypertensive drugs that are also well tolerated (Taylor et al., 2011).

In the same study by Taylor et al. (2011), ARBs have been shown to improve outcomes in a variety of conditions, including diabetic nephropathy, chronic heart failure or heart failure after a myocardial infarction, hypertension with left ventricular hypertrophy, and patients with a history of previous events or complicated diabetes who are at high cardiovascular risk. They concluded that ARBs can be used as first-line therapy or added at a later stage of treatment titration to treat hypertension. Because they combine modest blood pressure (BP) decrease with high tolerability and once-daily dosing, ARBs are appealing to both clinicians and hypertensive patients (Taylor et al., 2011).

As a matter of fact, ARBs are the most recent family of pharmaceuticals to be approved for use in the treatment of hypertension, either alone or in combination with other treatments (Ross & Papademetriou, 2004). The effectiveness of ARBs in decreasing blood pressure has been extensively documented (McFarlane, 2011). Because they fit both of these criteria, angiotensin receptor blockers have emerged as a prominent therapeutic class (effective and well-tolerated). According to numerous studies, all licenced angiotensin receptor blockers are extremely selective for angiotensin-1 receptors, decrease blood pressure as monotherapies, and perform effectively in combination with other medicines, especially diuretics (Ross & Papademetriou, 2004).

2.2 Benzimidazole

According to National Center for Biotechnology Information - PubChem (2021), benzimidazole is a heterocyclic aromatic organic compound with molecular formula, $C_7H_6N_2$. It is made up of benzene and imidazole that fused together.



Note. Orange circle: benzene; Green circle: imidazole.

Figure 2.0. The (i) 2D and (ii) 3D structure of benzimidazole compound with molecular formula, $C_7H_6N_2$ (National Center for Biotechnology Information – PubChem, 2021).

Benzimidazoles are heterocyclic aromatic compounds with a six-membered benzene moiety fused to a five-membered imidazole moiety as a structural feature (Gaba & Mohan, 2015). Molecules with benzimidazole motifs have shown promise in biological and clinical research. It is now a preferred moiety with numerous pharmacological properties, including

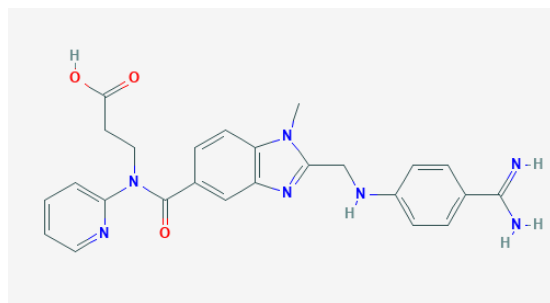
being a potent inhibitor of various enzymes involved in a wide range of therapeutic uses, including antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, and antihistamine, as well as cardiovascular disease, neurology, endocrinology, ophthalmology, and more (Shingalapur et al., 2010). Because of its good features, such as enhanced stability, bioavailability, and considerable biological activity, benzimidazole compounds have attracted a lot of attention (Kamanna, 2019).

From the same study by Kamanna (2019), thiabendazole was the first benzimidazole developed and licenced for human use in 1962, and more benzimidazole derivatives have been clinically approved since then. These include albendazole, mebendazole, and flubendazole as anthelmintics; omeprazole, lansoprazole, and pantoprazole as proton pump inhibitors; astemizole as antihistaminic; envirodine as antiviral. That is why benzimidazole nucleus containing pharmacophore has been extensively used in biological and clinical research in current drug discovery (Kamanna, 2019). As Ross and Papademetriou (2004), mentioned that a successful therapy must not only be effective, but also well tolerated.

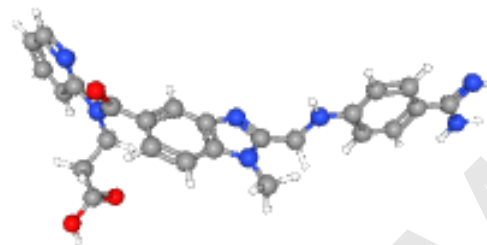
To prove this, Kamanna (2019), has highlighted in the same study that there are other therapeutic agents such as anticancer, antiproliferative, antimicrobials, antivirals, antiparasites, anthelmintic activity, anticonvulsant, antioxidants, anti-inflammatory, antihypertensive, immunomodulators, proton pump inhibitors, anticoagulants, hormone modulators, and CNS stimulants, as well as antidepressants, have been reported in the literature for various substituted derivatives of benzimidazole.

2.2.1 Dabigatran

According to National Center for Biotechnology Information - PubChem (2021), dabigatran is an anticoagulant and direct thrombin inhibitor with molecular formula, $C_{25}H_{25}N_7O_3$. This compound is commonly been used to prevent stroke and venous embolism in people with persistent atrial fibrillation. Dabigatran is an aromatic amide made by combining the carboxy group of 2-[(4-carbamimidoylphenyl)amino]methyl-1-methyl-1H-benzimidazole-5-carboxylic acid with the secondary amino group of N-pyridin-2-yl-beta-alanine in a formal condensation reaction. It is an anticoagulant that is used to prevent stroke and systemic embolism. Dabigatran etexilate is a prodrug that is taken orally and completely synthesized by carboxylesterases to the active form dabigatran. It acts as an anticoagulant, a thrombin inhibitor (EC 3.4.21.5), and a ribosyldihydronicotinamide dehydrogenase (quinone) inhibitor (EC 1.10.99.2). In summary from the PubChem (2021), dabigatran is an aromatic amide, a benzimidazole derivative, a carboxamidine, a pyridine derivative, and a beta-alanine derivative.



(i)



(ii)

Figure 2.1. The (i) 2D and (ii) 3D structure of dabigatran compound with molecular formula, $C_{25}H_{25}N_7O_3$ (National Center for Biotechnology Information – PubChem, 2021).

Dabigatran etexilate (also known as dabigatran) is a reversible, direct thrombin inhibitor (DTI) that may be used as an alternative to older and newer oral and parenteral anticoagulants for the treatment and prevention of thromboembolic disorders (Clemens et al., 2013). It is a prescription drug that helps to prevent and slow the formation of blood clots. The US Food and Drug Administration (FDA) has approved dabigatran etexilate as the first oral and reversible anticoagulant in the DTI class. When compared to previously available anticoagulants, dabigatran etexilate has shown to have a considerable clinical use. However, certain novel anticoagulants are still required for efficacy and safety (Hu & Liu, 2020). According to Koretsune et al. (2019), in individuals with non-valvular atrial fibrillation, dabigatran was the first direct oral anticoagulant licenced for stroke prevention.

On top of that, warfarin, the traditional anticoagulant, is ineffective at preventing new thromboses in arteries, but dabigatran is far more effective (Kasmeridis et al., 2013). Dabigatran is also being studied for a variety of clinical indications, and in some cases, it may be a better alternative to warfarin as the preferred orally administered anticoagulant (“blood thinner”) because it does not require frequent blood tests for international normalized ratio (INR) monitoring while providing similar efficacy. Unlike the traditional anticoagulant, warfarin, dabigatran has no specific means to reverse the anticoagulant effect in the event of a large bleeding episode (Hu & Liu, 2020). Moreover, for more than 50 years, heparins and vitamin K antagonists have been the principal anticoagulants used to treat various cardiovascular and thromboembolic illnesses. They are, however, difficult to administer and have a number of drawbacks (Kim et al., 2017).

According to Rago et al. (2017), DTIs were developed and studied in response to the need for new anticoagulants for the prevention and treatment of venous thromboembolism (VTE), heparin-induced thrombocytopenia (HIT), acute coronary syndromes (ACS), secondary prevention of coronary events after ACS, and non-valvular atrial fibrillation. Dabigatran works in the blood by inhibiting the clotting process by blocking the action of factor II (thrombin) of the blood coagulation cascade. It forms a direct univalent bond with the active site of thrombin, inactivating both fibrin-bound and unbound (i.e., free) thrombin. The bound thrombin can still cause thrombus formation. Unfractionated heparin and low-molecular-weight heparin are indirect thrombin inhibitors that cannot inhibit fibrin-bound thrombin. As

a coagulant, dabigatran offers a significant theoretical advantage over heparins (Hu & Liu, 2020).

2.2.2 Pimobendan

According to National Center for Biotechnology Information - PubChem (2021), pimobendan is a pyridazinone that belongs to the benzimidazole family. Its molecular formula is $C_{19}H_{18}N_4O_2$. This compound functions as a cardiotonic medication, a vasodilator, and a phosphoric diester hydrolase inhibitor (EC 3.1.4.*).

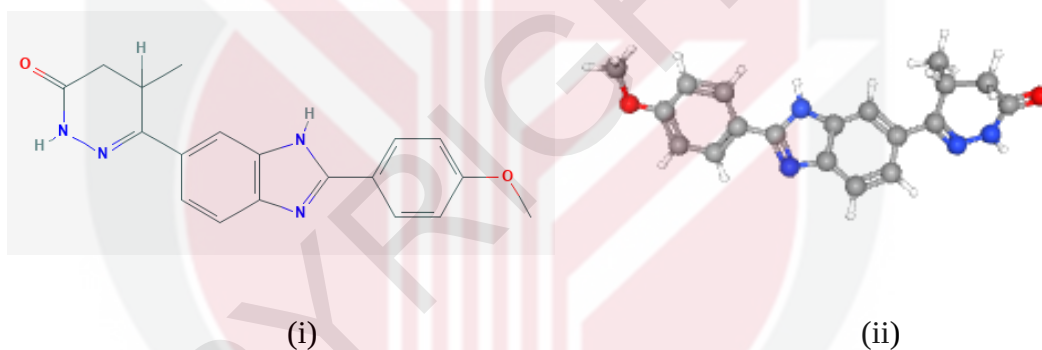


Figure 2.2. The (i) 2D and (ii) 3D structure of pimobendan compound with molecular formula, $C_{19}H_{18}N_4O_2$ (National Center for Biotechnology Information – PubChem, 2021).

Pimobendan is a novel calcium sensitizer that has both inotropic and peripheral vasodilating effects, which are due to cardiac myofilament sensitization to intracellular calcium and phosphodiesterase III inhibition (Chu et al., 1995). Besides, according to Kato (1997), pimobendan is a benzimidazole-pyridazinone derivative that has

inotropic and peripheral vasodilatory activities by inhibiting phosphodiesterase (PDE)-III and making cardiac contractile proteins more sensitive to calcium. Unlike other PDE-III inhibitors, this one improves cardiac contractility without increasing calcium release in the cytosol. To prove, there are a number of clinical trials have shown that a single oral or intravenous dose of pimobendan improves left and right ventricular performance in congestive heart failure patients.

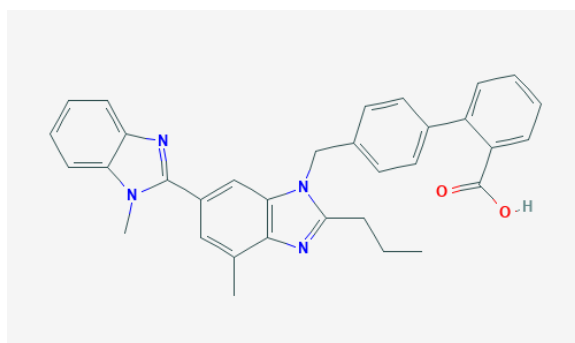
Takeda et al. (2001), had stated in a study that this drug is unique in that it improves cardiac contractility without raising cytosolic calcium release, which means it should not raise energy demand. Pimobendan is believed to be effective in the treatment of heart failure because the intracellular calcium concentration in the failing myocardium is reduced. The effect of long-term pimobendan administration in patients with mild to moderate chronic heart failure was investigated in this study. Not only for human, pimobendan is most commonly used in dogs as chewable tablets that contain 1.25 or 5 mg pimobendan per tablet and are administered orally at a total daily dose of 0.5 mg/kg body weight. It is an inotropic medication with vasodilator properties that is non-sympathomimetic and non-glycoside (Asif, n.d.).

Meanwhile in human, pimobendan has also been proven to be helpful as an add-on treatment in patients with moderate-to-severe chronic heart failure who are on diuretic and digitalis therapy, with or without vasodilator therapy, in several comparative clinical trials. As a result, pimobendan may be predicted to reduce the amount of energy required by the failing heart, making it useful in the treatment of

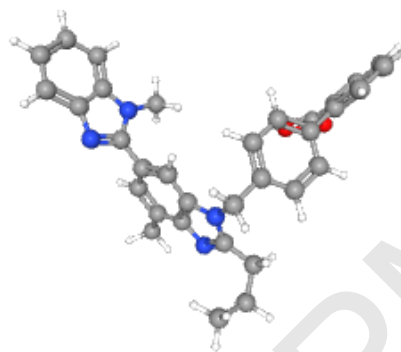
heart failure patients (Kato, 1997). For instance, in the same research, they reported that pimobendan 2.5 mg b.i.d. (taken twice a day) was well tolerated and had the greatest efficacy as an add-on medication for patients with acute and chronic heart failure. The findings of the research revealed that pimobendan could be effective in the treatment of heart failure patients. However, as many researchers have pointed out, significant treatment end-points in congestive heart failure are increasingly aimed not only at symptom relief and improved quality of life, but also at life extension.

2.2.3 Telmisartan

According to National Center for Biotechnology Information - PubChem (2021), telmisartan is a non-peptide angiotensin II receptor antagonist with antihypertensive properties that is derived from benzimidazole class of drugs. Angiotensin II binding to the AT1 subtype receptor, which is found in vascular smooth muscle and the adrenal gland, is selectively blocked by telmisartan. The antagonism causes vasodilation and inhibits angiotensin II-mediated aldosterone synthesis, resulting in a decrease in salt and water excretion as well as an increase in potassium excretion, lowering blood pressure. In summary from the PubChem (2021), telmisartan is used to treat hypertension as angiotensin II receptor blocker. It functions as an antihypertensive, angiotensin receptor antagonist, an inhibitor of EC 3.4.15.1 (peptidyl-dipeptidase A), a xenobiotic, and an environmental pollutant. It is a carboxybiphenyl, a biphenyl, and a member of the benzimidazole family. The molecular formula of telmisartan is $C_{33}H_{30}N_4O_2$.



(i)



(ii)

Figure 2.3. The (i) 2D and (ii) 3D structure of telmisartan compound with molecular formula, $C_{33}H_{30}N_4O_2$ (National Center for Biotechnology Information – PubChem, 2021).

Telmisartan is an ARB that was licenced by the Food and Drug Administration (FDA) in November 1998 for the treatment of hypertension. When compared to other agents, it has been shown to provide effective and long-lasting blood pressure management (McFarlane, 2011). In addition to the fact that telmisartan (Micardis, Pritor), a well-known angiotensin type 1 receptor antagonist, is approved in the EU for the treatment of hypertension and the reduction of cardiovascular morbidity in patients with manifest atherothrombotic cardiovascular disease (CVD) or type 2 diabetes mellitus with documented target organ damage (Frampton, 2011). Telmisartan, on the other hand, is the first ARB to show promise in lowering cardiovascular risk in patients at high risk (McFarlane, 2011). Telmisartan can be regarded an effective therapy choice for CVD prevention in

people with a high vascular risk based on these findings and becoming well-known ARB that can be taken once a day orally (Frampton, 2011).

According to the study by Foulquier et al. (2014), in both hypertension and non-hypertensive individuals, systolic blood pressure (SPBs) were lower in telmisartan-treated patients compared to patients treated with placebo (standard treatment without an ARB) throughout the research. A meta-analysis of 28 randomised controlled trials involving 5157 patients found that telmisartan had better blood pressure management, fewer drug-related side events, and better tolerance in hypertensive patients than various ACE inhibitors (enalapril, ramipril, and perindopril). When compared to losartan, telmisartan resulted in a significant reduction in diastolic and systolic BP, as well as a significant reduction in 24-hour mean ambulatory BP, according to another meta-analysis of eleven studies comprising 1832 participants (McFarlane, 2011). In short, telmisartan is approved in the EU for the treatment of essential hypertension in adults as monotherapy (Frampton, 2011).

2.2.4 Candesartan

According to National Center for Biotechnology Information - PubChem (2021), candesartan with molecular formula, $C_{24}H_{20}N_6O_3$ is an antihypertensive angiotensin II receptor antagonist produced from benzimidazoles. The prodrug of candesartan is candesartan cilexetil. Candesartan cilexetil is entirely metabolised to

candesartan when ingested. Candesartan blocks angiotensin II-mediated vasoconstriction and induces vasodilation by specifically competing with angiotensin II for the binding of the angiotensin II receptor subtype 1 (AT1) in vascular smooth muscle. Antagonism of AT1 in the adrenal gland also inhibits angiotensin II-stimulated aldosterone synthesis and secretion by the adrenal cortex, resulting in a rise in salt and water excretion, as well as a decrease in plasma volume and blood pressure. In general, angiotensin II receptor blocker candesartan is commonly used in the treatment of hypertension and heart failure. Furthermore, candesartan is a benzimidazolecarboxylic acid with an ethoxy group at position 2 and a (2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl) group at position 1. It functions as an antihypertensive, an angiotensin receptor antagonist, a pollutant in the environment, and a xenobiotic. It is also a biphenyltetrazole and a benzimidazolecarboxylic acid.

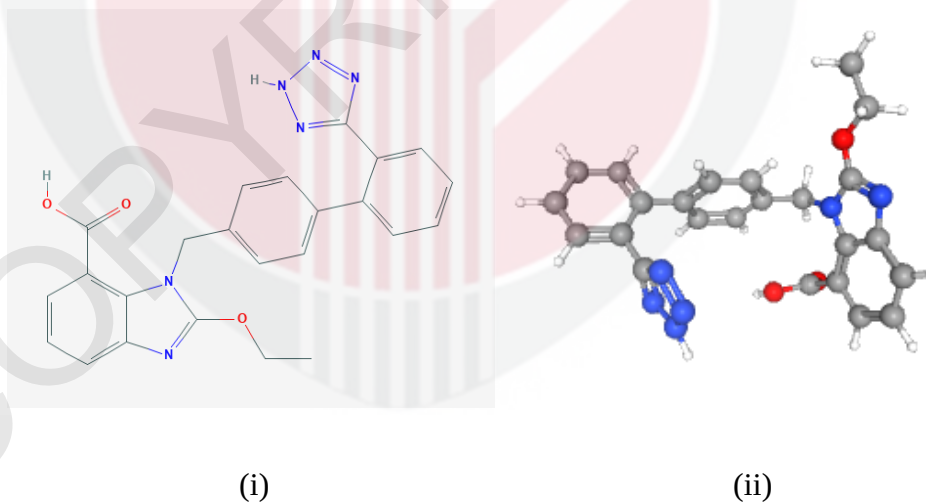


Figure 2.4. The (i) 2D and (ii) 3D structure of candesartan compound with molecular formula, $C_{24}H_{20}N_6O_3$ (National Center for Biotechnology Information – PubChem, 2021).

Candesartan cilexetil (Atacand®, AstraZeneca) is an angiotensin II type 1 (AT1) receptor antagonist that is extremely selective and potent (Fukui et al., 2003). It is an angiotensin-converting enzyme inhibitor with unbeatable binding qualities to the angiotensin-1 receptor, a lengthy duration of action, and increased efficacy. The heart, kidney, vascular smooth muscles, adrenal gland, brain, platelets, and adipocytes all have AT1 receptors. They cause vasoconstriction, salt retention, renin secretion suppression, vascular and cardiac fibrosis stimulation, increased myocardial contractility, and sympathetic activity activation. Candesartan binds irreversibly to the AT1 receptor, blocking AT II effects (Ross & Papademetriou, 2004). Thus, it is believed to be a long-acting selective antagonist that binds to AT1 receptors with a high affinity (Matsumori, 2003).

In relation to that, according to the same study by Ross and Papademetriou (2004), candesartan has been studied in the management of hypertension, stroke prevention and treatment, renal protection, and heart failure. Stroke protection has also been demonstrated in studies, notably in patients with isolated systolic hypertension. More recent evidence suggests that candesartan cilexetil is effective in the treatment of heart failure patients and highly effective in lowering blood pressure (Fukui et al., 2003). For that reason, candesartan monotherapy has been shown to be safe and effective in people with hypertension (Ross & Papademetriou, 2004).

2.3 Systematic Review/Meta-Analysis

Systematic reviews (SR) and meta-analyses (MA) have been increasingly popular in recent years in a variety of sectors. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was issued in 2009, and it has tremendously aided in the standardisation and improvement of systematic reviews and meta-analyses (Ahn & Kang, 2018).

As reported by Sriganesh et al. (2016), systematic reviews are conducted to gather all available data to answer a specific clinical question, and they entail a repeatable and thorough search of the literature as well as critical appraisal of studies that meet the criteria. It gathers all relevant research on a certain topic and design, then evaluates and synthesises their findings (Ahn & Kang, 2018). According to Gopalakrishnan and Ganeshkumar (2013), the goal of systematic reviews is to discover, assess, and synthesise the findings of all relevant individual research on a health-related topic, making the available information more accessible to decision-makers. To this aim, systematic reviews may or may not include a statistical synthesis known as meta-analysis, depending on how comparable the studies are and whether integrating their results is useful.

Hence, to develop a systematic review, it begins with a clinical question and a protocol that includes clear objectives, outcomes, and a well-thought-out plan for data analysis and reporting. It is highly recommended that protocols be registered in a publicly accessible database such as PROSPERO. This boosts reader confidence in the study's

findings by allowing for transparency (Sriganesh et al., 2016). In addition to that, Sriganesh et al. (2016) also had mentioned that a thoroughly conducted systematic reviews, when combined with a meta-analysis (quantitative pooling of results from individual trials), gives the best available evidence for informing clinical practise. Systematic review can be either qualitative (summarising eligible research) or quantitative (meta-analysis), which statistically combines data from separate studies. Meta-analyses are not always the outcome of SRs. Similarly, not all meta-analyses may have been preceded by an SR, despite the fact that this is a necessary component to ensure that conclusions are not influenced by selection bias (Sriganesh et al., 2016).

Based on study by Ahn and Kang (2018), a meta-analysis is a way of examining and combining different results that is valid, objective, and scientific. It is usually conducted on randomised controlled trials (RCTs) with a high degree of evidence in order to generate more trustworthy results. The basic premise of meta-analysis is that it decreases the amount of data by combining data from numerous sources and aids in the planning of research as well as the formulation of guidelines. It also aids in the efficient use of existing data by guaranteeing generalizability, assisting in the verification of relationship consistency, explaining data discrepancy, and quantifying the data. Using explicit approaches, it aids in improving the precision of risk estimation (Gopalakrishnan & Ganeshkumar, 2013). The goal of a meta-analysis is to arrive at a result with greater power and precision than individual studies might provide. As a result, it is critical to assess the direction of impact, size of effect, homogeneity of effects across trials, and quality of evidence prior to analysis (Ahn & Kang, 2018). Meanwhile, Haidich (2010), concluded that meta-analysis is a quantitative review in which

the clinical effectiveness of treatments is assessed by generating the weighted pooled estimate for at least two studies. A forest plot is used to describe the pooled estimate, which is the result of the meta-analysis.

As a result, the phrase "systematic review" will refer to the full process of gathering, reviewing, and presenting all available evidence, whereas "meta-analysis" will refer to the statistical approach used to extract and combine data to provide a summary result (Gopalakrishnan & Ganeshkumar, 2013). However, a lack of knowledge regarding systematic reviews and meta-analyses might lead to erroneous conclusions being drawn from the review and analytic processes (Ahn & Kang, 2018).

CHAPTER 3

METHODOLOGY

3.1 Identification

3.1.1 Research Question

The systematic review/meta-analysis was performed according to the PRISMA statements (Page et al., 2021). PRISMA statement is a minimum set of elements for systematic reviews and meta-analyses that is based on evidence. PRISMA is generally designed for reporting reviews that evaluate the effects of interventions, although it can also be used to record systematic reviews with goals other than evaluating interventions. In relation to that, this study was started with developing research question to achieve the specific objectives and identify what kind of research to be conducted. This would guide the researcher to the objectives throughout the study.

3.1.2 Eligibility Criteria

The inclusion criteria of the study have been identified which by following the components of PICOS model. PICOS stands for patient/population, intervention, comparison, outcomes and study design. The PICOS model is frequently used to construct a systematic review's search strategy (Frandsen et al., 2020).

3.1.2.1 Population

All adult patients with a variety of age were included in this study. There were no restrictions applied in terms of age, gender, and racial status. All studies must include participants that experienced any cardiovascular events or any condition related to heart disease after consuming benzimidazole.

3.1.2.2 Intervention

The included study must involve the administration of drug which derived from benzimidazole by orally. These drugs were the one that being used for treating cardiovascular diseases. The included drugs were dabigatran, pimobendan, telmisartan and candesartan cilexetil.

3.1.2.3 Comparator

These benzimidazole compounds as mentioned above, were being compared with non-benzimidazole drugs such as warfarin and other chemical compounds that were established to be effectively used in managing the cardiovascular disease. The placebo also was included as comparator to benzimidazole compounds.

3.1.2.4 Outcome

The primary outcome of this study was the positive effect of the drugs towards CVD patients or the progression of the cardiovascular conditions towards the patients that taking the drugs. Whilst the secondary outcomes were the incidence of cardiovascular events and the side effects of the benzimidazole drugs if any. We used Review Manager (RevMan) version 5.4 software to measure the numerical data obtained from the articles. The outcome of this study was further sub-divided into three cardiovascular conditions: low, medium and high risk of cardiovascular patients to measure the potentiality of benzimidazole drugs in treating or managing cardiovascular conditions at any stages.

3.1.2.5 Study Design

All types of study designs that involved human as subjects were included in this study. These included Randomized Controlled Trial (RCT) and non-RCT studies such as cohort study and case report. These studies were crucial and beneficial to provide the overview or overall outcomes pertaining to the benzimidazole drugs for CVD.

3.1.3 Search Strategy

The keyword for the article search was developed based on the PICOS model. There were five databases used to run the keywords including PubMed, Scopus, Cochrane Library, Wiley Online Library and Emerald Insights. The keyword was (benzimidazole) AND (heart OR "heart disease*" OR cardiovascular OR "cardiovascular disease*") AND (type* OR risk*) AND (adult* OR patient*) AND (oral*). Language, document type and publication years were not restricted. No limitation was applied throughout the article searching.

3.2 Selection

3.2.1 Article Search

The articles were obtained from the database searching. All the collected articles were imported into Java, Alver, Batada, Reference (JabRef) as reference manager tool. This tool removed the duplicates articles from the five databases. Then, all the number of articles to be included in this study were recorded in a flowchart starting from the first screening up until the last article screening.

3.2.2 Title and Abstract Screening

The first screening was being done on the title of the articles which only related to the study. At this stage, most articles were excluded if not mentioning at all

the keywords used in this study. Next, the abstracts were screened according to the contents that could only provide the information or explanation related to the research question.

3.2.3 Full Text Screening

The last screening was done by reviewing the full text version of the articles. Only the articles that consisted of all the inclusion criteria were included in this study. Reasons for excluding the studies would be recorded. This last step screening would allow the researcher to further undergo the data extraction and data analysis.

3.3 Appraisal

3.3.1 Data Extraction

From the included studies, all the relevant data that followed the objectives of this study, were extracted out and being recorded in the Google Spreadsheet Online or Excel format in table form. The data extraction was conducted critically to be used in data analysis. The extracted data included authors, years, countries, number of populations, adult ages, study design, risk type and lastly, the overall outcomes.

3.3.2 Quality Assessment

This assessment was performed by referring to the checklist from the Alberta Heritage Foundation for Medical Research (AHFMR). This step was important to assess the quality of the articles included in this study that determined the reliability of the data obtained from each article. AHFMR is a standard quality assessment for evaluating research papers that provides checklist for assessing the quality of qualitative and quantitative studies (Leanne et al., 2004). In this study, 14 items were scored based on the degree to which the specific criteria were met (“yes” = 2, “partial” = 1, “no” = 0). Items that did not apply to a particular study design were marked “N/A” and were excluded from the calculation of the total score. A summary score was calculated for each paper by summing the total score obtained across relevant items and dividing by the total score of 28 (for interventional study) or 22 (non-interventional study). Lastly, the percentage of the total summary score was calculated for each article.

3.4 Synthesization

3.4.1 Analysis of Data

For numerical data, the analysis was being conducted by using the RevMan version 5.4 tool to clearly distinguish the potential effectiveness between benzimidazole and other compounds in managing the cardiovascular conditions. Whereas for article that could not provide the data for the RevMan analysis, the

outcomes of the studies were then being analyzed and interpreted according to the research question of this study.

3.4.2 Outcome and Conclusion

All the results obtained from this were presented in the form of tables and figures including the forest plot. All variability of the findings obtained from the data analysis were recorded and synthesized into one summary.

CHAPTER 4

RESULT

4.1 Literature Search

The keywords used as search item were (benzimidazole) AND (heart OR "heart disease*" OR cardiovascular OR "cardiovascular disease*") AND (type* OR risk*) AND (adult* OR patient*) AND (oral*). A total of 1033 studies were retrieved from 5 databases whereby 3 were from Emerald Insight, 19 were from Cochrane Library, 159 were from Scopus, 194 were from PubMed and 658 were from Wiley Online Library. 232 studies were removed as duplicates that having the similar titles and contents. Thus, the remaining 801 studies were screened by title and abstract according to the eligibility criteria. After screening, 553 studies were excluded, and the remaining 248 studies were further reviewed in full-text assessment. Eventually, 219 studies were excluded as they did not meet the described eligibility criteria. 29 remaining studies were subjected to systematic review/meta-analysis in their respective category of study. All these number of articles records were summarized in a flow chart below.

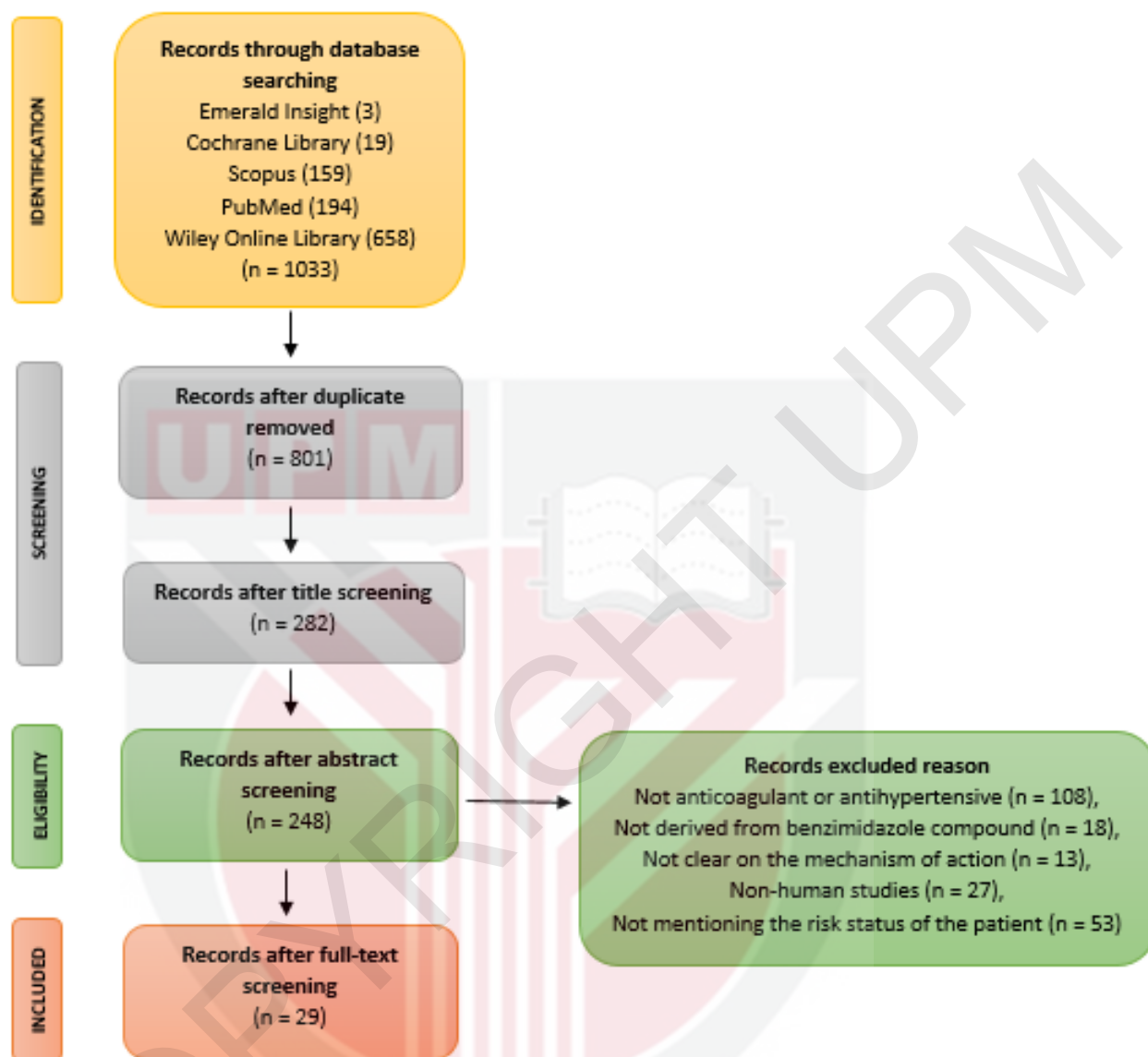


Figure 4.1. Flow of literature search according to the PRISMA guidelines.

4.2 Data Findings

A systematic review/meta-analysis was done to observe the effectiveness of benzimidazole drugs compound to be used for cardiovascular disease patients. The study population and study design used in every article were stated in Table 4.2 (a). The details of the drugs included in this study were stated as shown in Table 4.2 (b) and (c). By referring to Table 4.2 (b), it can be seen that there were list of comparison between benzimidazole and non-benzimidazole drug as anticoagulant or antihypertensive for CVD. In this study, for anticoagulant agent, dabigatran is made from benzimidazole compound which was being compared with non-benzimidazole compound that consist of warfarin, rivaroxaban and apixaban. Whereas, for antihypertensive agent, pimobendan, telmisartan and candesartan were made up of benzimidazole compound that being compared with non-benzimidazole compound which were lisinopril, valsartan, nisoldipine, irbesartan, rosuvastatin and ramipril. The IUPAC nomenclature provided in Table 4.2 (b) were used to get an overview towards the structure of the compound-derived for respective drugs. While Figure 4.2 shows the number of articles included for this systematic review which consist of interventional and non-interventional study.

Table 4.2 (a). The study population and study design.

Drugs	Included study	Number of subjects (n)	Country	Age (years)	Study design
Dabigatran	Hu & Liu (2020)	NM	USA	NM	Descriptive study
	Akgullu et al. (2013)	1	Turkey	41	Case report
	Arachchillage & Cohen (2013)	NM	UK	≥18	Observational study

	Kasmeridis et al. (2013)	18113	UK	65-75	Observational study
	Larock et al. (2014)	69	Belgium	≥65	Prospective cohort study
	Nagao et al. (2015)	363	Japan	<75	Retrospective cohort study
	Olesen et al. (2014)	18611	Denmark	30-100	RCT
	Stepanyan et al. (2014)	301	USA	61 ± 10.4	Retrospective cohort study
	Winkle et al. (2014)	1745	USA	63.6 ± 9.8	Retrospective cohort study
	Alcusky et al. (2018)	710	USA	≥65	Retrospective cohort study
	Amin et al. (2019)	63206	USA	≥65	Retrospective cohort study
	Amin et al. (2019) - 2	198171	USA	≥65	Retrospective cohort study
	Beshir et al. (2017)	478	Malaysia	≥18	Retrospective cohort study
	Chang et al. (2015)	46163	USA	≥18	Retrospective cohort study
	Deitelzweig et al. (2019)	88582	USA	≥80	Retrospective cohort study
	Koretsune et al. (2019)	326	Japan	≥18	Retrospective cohort study
	O'Brien et al. (2016)	10133	USA	≥18	Prospective cohort study
	Rago et al. (2017)	1	Italy	45	Case report
	Villines et al. (2019)	12763	USA	≥18	Retrospective cohort study
Pimobendan	Chu et al. (1995)	8	China	55 ± 9	RCT
	Bajcetic et al. (2007)	37	Germany	59.0 ± 7	RCT
	Chang et al. (2016)	15	China	NM	Prospective cohort study
Telmisartan	Moon et al. (2019)	57	Republic of Korea	19-50	Cohort study
	Bohm et al. (2017)	30937	*40 countries	≥55	Observational study

	Israili (2000)	NM	USA	NM	Descriptive study
	Neldam & Edwards (2009)	639	UK	57	RCT
	Matsumori (2003)	305	Japan	≥20	RCT
Candesartan cilexetil	Israili (2000)	NM	USA	NM	Descriptive study
	Fukui et al. (2003)	NM	Japan	20-85	Prospective cohort study
	McInnes et al. (2000)	237	UK	20-80	RCT
NM = not mention, RCT = randomized-controlled trial, UK = United Kingdom, USA = United States of America					
*Not mentioned specifically					

Table 4.2 (b). List of benzimidazole drugs and non-benzimidazole drugs to be included in this study.

Types of drug	Category	Name of drug	IUPAC name	Included study
Anticoagulant	Benzimidazole	Dabigatran	3-[[2-[(4-carbamimidoylanilino)methyl]-1-methylbenzimidazole-5-carbonyl]-pyridin-2-ylamino]propanoic acid	Hu & Liu (2020), Akgullu et al. (2013), Arachchillage & Cohen (2013), Kasmeridis et al. (2013), Larock et al. (2014), Nagao et al. (2015), Olesen et al. (2014), Stepanyan et al. (2014), Winkle et al. (2014), Alcusky et al. (2018), Amin et al. (2019), Beshir et al. (2017), Chang et al. (2015), Deitelzweig et al. (2019), Koretsune et al. (2019), O'Brien et al. (2016), Rago et al. (2017), Villines et al. (2019)
		Warfarin	4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one	Arachchillage & Cohen (2013), Kasmeridis et al. (2013), Olesen et al. (2014), Stepanyan et al. (2014), Winkle et al. (2014), Amin et al. (2019), Deitelzweig et al. (2019), O'Brien et al. (2016), Villines et al. (2019)
	Non-benzimidazole	Rivaroxaban	5-chloro-N-[[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methyl]thiophene-2-carboxamide	Arachchillage & Cohen (2013), Kasmeridis et al. (2013), Olesen et al. (2014), Stepanyan et al. (2014), Winkle et al. (2014), Amin et al. (2019), Deitelzweig et al. (2019), O'Brien et al. (2016), Villines et al. (2019)
		Apixaban	1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5-dihydropyrazolo[3,4-c]pyridine-3-carboxamide	Arachchillage & Cohen (2013), Kasmeridis et al. (2013), Olesen et al. (2014), Amin et al. (2019), Deitelzweig et al. (2019), Villines et al. (2019)

Antihypertensive	Benzimidazole	Pimobendan	3-[2-(4-methoxyphenyl)-3H-benzimidazol-5-yl]-4-methyl-4,5-dihydro-1H-pyridazin-6-one	Chu et al. (1995)
		Telmisartan	2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl]phenyl]benzoic acid	Bajcetic et al. (2007), Chang et al. (2016), Moon et al. (2019), Bohm et al. (2017), Israili (2000), Neldam & Edwards (2009)
		Candesartan cilexetil	1-cyclohexyloxycarbonyloxyethyl 2-ethoxy-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylate	Matsumori (2003), Israili (2000), Fukui et al. (2003), McInnes et al. (2000)
	Non-benzimidazole	Lisinopril	(2S)-1-[(2S)-6-amino-2-[[[(1S)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid	McInnes et al. (2000)
		Valsartan	(2S)-3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]amino]butanoic acid	Israili (2000)
		Nisoldipine	3-O-methyl 5-O-(2-methylpropyl) 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	Bajcetic et al. (2007)
		Irbesartan	2-butyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one	Israili (2000)
		Rosuvastatin	(E,3R,5S)-7-[4-(4-fluorophenyl)-2-[methyl(methylsulfonyl)amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid	Moon et al. (2019)

Ramipril

(2S,3aS,6aS)-1-[(2S)-2-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-3,3a,4,5,6,6a-hexahydro-2H-cyclopenta[b]pyrrole-2-carboxylic acid

Bohm et al. (2017)

Table 4.2 (c). Benzimidazole drugs and their mechanism of action as anti-cardiovascular agent.

Benzimidazole drug	Function	Mechanism of action
Dabigatran	Anticoagulant	Blood-thinner
Pimobendan	Antihypertensive	Vasodilator
Telmisartan	Antihypertensive	Angiotensin-receptor blocker (ARB)
Candesartan cilexetil	Antihypertensive	Angiotensin-receptor blocker (ARB)

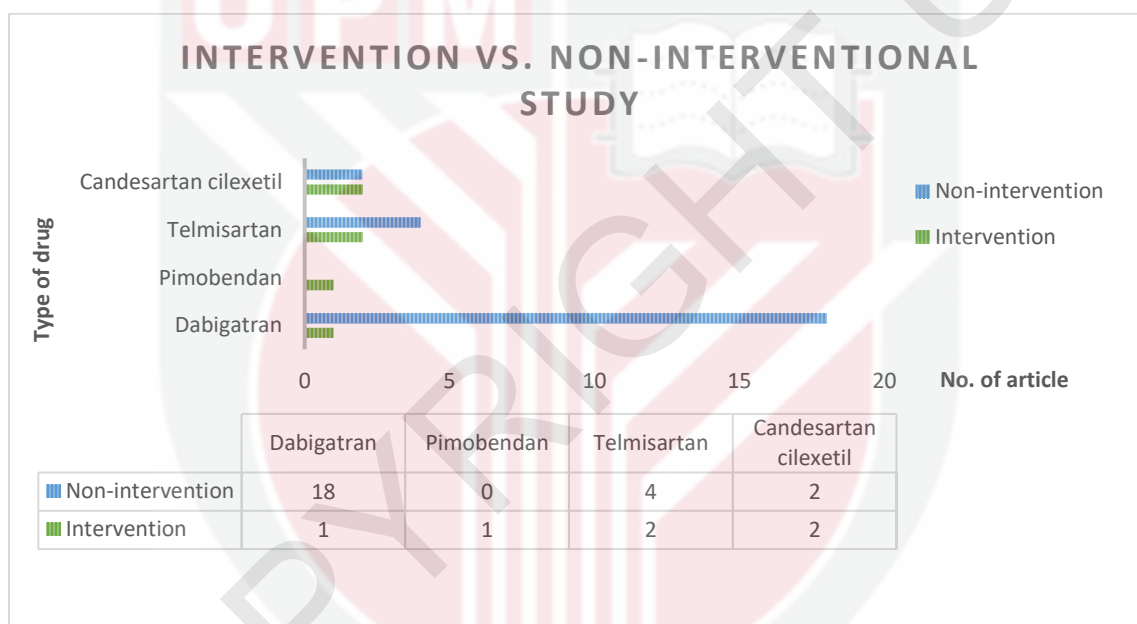


Figure 4.2. Bar chart of summarizing the number of articles for all four-types of benzimidazole drugs which consisted of interventional and non-interventional studies.

4.3 Data Extraction

Table 4.3.1 (a) summarized the outcome of the benzimidazole drugs in comparison to non-benzimidazole drugs in measuring the effectiveness towards improving the conditions for cardiovascular patients. Meanwhile, Table 4.3.2 (a-c) were tabulated for conducting the meta-analysis to measure the effectiveness of benzimidazole drugs against the non-benzimidazole drugs in managing the cardiovascular conditions. The positive effects indicate that the drug exhibited its effectiveness towards CVD patients.

Table 4.3.1 (a). Outcome of CVD patients for all-four types of benzimidazole drugs.

Drugs	Included study	Outcome
Dabigatran	Hu & Liu (2020)	As coagulants, dabigatran has a significant theoretical advantage over heparins. Warfarin, the traditional anticoagulant, is ineffective at preventing new thromboses in arteries, whereas dabigatran is far more effective. Dabigatran is an alternative to warfarin as the preferred orally administered anticoagulant (“blood thinner”) in some cases because it does not require repeated blood testing for international normalized ratio (INR) monitoring thus providing comparable efficacy results. Unlike the classic anticoagulant, warfarin, dabigatran has no clear way to reverse the anticoagulant effect in the event of a significant bleeding event.
	Akgullu et al. (2013)	Dabigatran was compared to warfarin in the mainstay RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) research in the treatment of patients with non-valvular atrial fibrillation (NVAf). The researchers found that dabigatran at a dose of 110 mg and warfarin both caused thromboembolic events at comparable rates in the RE-LY trial. Higher doses (150 mg) of dabigatran, on the other hand, resulted in lower rates of thromboembolic events. In the same research, it was discovered that twice-daily doses of 110 mg dabigatran resulted in less bleeding than warfarin.

Arachchillage & Cohen (2013)	Long-term anticoagulation with an oral vitamin K antagonist (VKA), such as warfarin, is the current standard of care for thrombotic antiphospholipid syndrome (APS). Warfarin, on the other hand, has a restricted therapeutic range, a gradual onset/offset of action, variable reaction, constant laboratory testing, and numerous experiences with food, drugs, and alcohol. In addition to these drawbacks, interactions between antiphospholipid (aPL) and warfarin make controlling anticoagulant effects difficult in patients with APS. New oral anticoagulants (NOACs) are theoretically a significant advancement because they do not require regular anticoagulant monitoring (although renal function should be monitored), have no recorded food or alcohol interactions, and have few reported drug interactions.
Kasmeridis et al. (2013)	OACs (direct thrombin inhibitors and direct factor Xa inhibitors) are a new oral anticoagulant that has recently been approved for the prevention of atrial fibrillation (AF)-related thromboembolism. In clinical trials, these drugs were shown to be at least as successful and safe as VKAs, and they are expected to fully change AF management. The latest OACs vary greatly from one another, allowing clinicians to tailor anticoagulation to the specific needs of each patient. Dabigatran 150 mg twice daily, for example, reduced ischemic stroke. Only if the latest drugs are used correctly will they be functional, safe, and cost-effective.
Larock et al. (2014)	In patients with NVAF, inappropriate use of dabigatran and rivaroxaban is common, and it can lead to serious side effects. It is important to reinforce health-care practitioners' and patients' education. Collaboration with clinical pharmacists will help you get the most out of your medication.
Nagao et al. (2015)	Uninterrupted dabigatran therapy in catheter ablation (CA) for AF tends to be a safe and efficient anticoagulant therapy that is comparable to continuous warfarin; however, while using dabigatran during CA, it is important to pay careful attention to the APTT values.
Olesen et al. (2014)	Dabigatran is the most commonly prescribed anticoagulant, but rivaroxaban and apixaban are becoming more popular. Patients who are started on rivaroxaban or apixaban have a greater risk of stroke and bleeding than those who start on warfarin or dabigatran. Age, female gender, and previous stroke were some of the variables linked to NOAC use vs. warfarin, while chronic

	kidney disease, myocardial infarction, and heart failure were linked to the reverse.
Stepanyan et al. (2014)	The use of peri-procedure dabigatran or rivaroxaban compared to uninterrupted warfarin did not result in a rise in bleeding or thromboembolic (TE) complications in this community of AF patients undergoing CA.
Winkle et al. (2014)	The rate of peri-procedural groin, hemorrhagic, and thromboembolic complications was extremely low when using disrupted OAC, low goal intraprocedural activated clotting time (ACT), and irrigated-tip radiofrequency (RF). Among OACs, there were only minor variations. Pre-ablation, low-risk patients can continue to take aspirin with no OAC. Moving from one OAC pre-ablation to another post-ablation is not an issue. The occurrence of neurologic events was not variable between dabigatran and warfarin.
Alcusky et al. (2018)	After an ischemic stroke, older adults treated with direct-acting oral anticoagulants have a wide range of outcomes depending on the treatment and dose.
Amin et al. (2019)	Apixaban use was linked to a lower risk of stroke/systemic embolism (SE), major bleeding (MB), and major adverse cardiac events (MACE) as compared to warfarin; dabigatran was linked to a lower rate of MACE; and rivaroxaban was linked to a lower rate of stroke/SE, MACE, and MB but a higher rate of MB.
Amin et al. (2019) - 2	Apixaban and rivaroxaban had lower risk of stroke/SE than warfarin, while dabigatran had a similar risk. Apixaban and dabigatran had lower MB and NCO risks, while rivaroxaban had a higher MB risk and a similar NCO risk. Apixaban had a lower risk of stroke/SE, MB, and NCO than warfarin; dabigatran had a lower risk of MB and NCO than warfarin; and rivaroxaban had a lower risk of stroke/SE but a higher risk of MB than warfarin. When opposed to warfarin, both DOACs had a lower risk of MACE. In summary, as compared to warfarin, DOACs were associated with a lower to equivalent risk of stroke/SE and MACE in the elderly Medicare population with NVAF, but with differing comparable risks for MB and net clinical outcome (NCO).
Beshir et al. (2017)	Although the risk of death from dabigatran-induced major bleeding episodes is low, these side effects have a high fatality

	rate. Older patients with a history of bleeding or congestive heart failure should be targeted for preventative steps.
Chang et al. (2015)	While rates of gastrointestinal bleeding appear to be comparable in this commercially insured sample of adults in the United States, we cannot rule out a 50% increase in the risk of gastrointestinal bleeding with dabigatran compared to warfarin or a more than two-fold higher risk of bleeding with rivaroxaban. Those who took dabigatran had the highest rate of gastrointestinal bleeding, while those who took rivaroxaban had the lowest rate. There was no statistically significant difference in the incidence of gastrointestinal bleeding between dabigatran and warfarin users, or between rivaroxaban and warfarin users, after accounting for possibly misleading covariates.
Deitelzweig et al. (2019)	Apixaban, dabigatran, and rivaroxaban were linked to a lower risk of stroke/SE as compared to warfarin. Apixaban was linked to a lower risk of MB, while dabigatran was linked to a similar risk and rivaroxaban was linked to a higher risk as compared to warfarin. When compared to dabigatran and rivaroxaban, apixaban was linked to a lower risk of stroke/SE and MB. When compared to rivaroxaban, dabigatran was linked to a lower risk of MB. When compared to warfarin, NOACs were associated with lower rates of stroke/SE and differing rates of MB in very old NVAf patients.
Koretsune et al. (2019)	In Japanese patients with NVAf, dabigatran was linked to a lower risk of stroke, systemic embolism, intracranial bleeding, and severe bleeding as compared to warfarin.
O'Brien et al. (2016)	In a recent AF cohort, Medicaid patients were not substantially less likely than others to use OACs overall or NOACs. Medicaid patients, on the other hand, spent less time in the therapeutic range than people with other types of insurance.
Rago et al. (2017)	The current case is the first to record full resolution of left atrial appendage thrombosis with oral dabigatran etexilate in a diabetes mellitus 1 (DM1) patient with AF who was scheduled for TEE-guided direct electrical cardioversion. Because of their variable cognitive impairment and inadequate compliance with periodic international normalized ratio (INR) control, NOAC therapy should be particularly beneficial in this group of patients. Dabigatran etexilate, a direct thrombin inhibitor, has emerged as one of the first new generation oral anticoagulants

		that could potentially replace warfarin in preventing arterial TE in patients with AF.
	Villines et al. (2019)	In this study, dabigatran was associated with a slightly lower major bleeding risk than rivaroxaban in NVAf patients who were newly started on standard-dose DOAC therapy, but no important difference in stroke risk. The smaller sample size for dabigatran vs. apixaban made it difficult to draw concrete conclusions.
Pimobendan	Chu et al. (1995)	Echocardiography was used to assess the pharmacodynamic effect of pimobendan. The ejection fraction, circumferential fiber shortening mean velocity, aortic flow peak velocity, cardiac index, and stroke volume index all increased by 50% to 60%. The end-systolic dimension of the left ventricle, systolic blood pressure, and diastolic blood pressure all decreased by 8% to 11%. For more than 8 hours, 5 milligrams (mg) of pimobendan improved cardiac efficiency. The pharmacodynamic effect accumulated despite the fact that there was no dose accumulation after repeated dosing. Starting with 5 mg once a day seems to be reasonable.
	Bajcetic et al. (2007)	The findings of this study strongly indicate that taking nisoldipine at the same time as telmisartan increases telmisartan bioavailability in hypertensive patients. Larger crossover studies will be required to confirm these findings and determine if the interaction of the two drugs affects the effectiveness and tolerability of telmisartan in clinical use.
	Chang et al. (2016)	Both longitudinal and circumferential stresses in diabetic patients improved after treatment with telmisartan. Via the PPAR/STAT3 pathway, telmisartan reduced hyperglycemia-induced cardiac fibrosis.
Telmisartan	Moon et al. (2019)	The pharmacokinetic parameters of telmisartan/amlodipine met the pharmacokinetic equivalent requirements, but not those of rosuvastatin. In practice, the rise in systemic rosuvastatin exposure caused by telmisartan/amlodipine co-administration will not be clinically important. However, to validate the findings of this analysis, a properly designed two-sequence crossover study is needed.
	Bohm et al. (2017)	Except for myocardial infarction and stroke, a mean reached systolic blood pressure (SBP) less than 120 mm Hg during treatment was linked to an increased risk of cardiovascular outcomes. Diastolic blood pressure (DBP) less than 70 mm Hg

		was associated with an increased risk of myocardial infarction and hospitalization for heart failure. Treatment-induced very low blood pressure was linked to an increased risk of multiple cardiovascular disease events. While it is impossible to rule out the possibility of reverse causality, these findings indicate that the lowest blood pressure possible is not always the best target for high-risk patients.
	Israili (2000)	Angiotensin II receptor blockers (ARBs) are a relatively new class of orally active antihypertensive drugs that are both effective and well tolerated. Therapy with ARBs has benefits that go beyond blood pressure regulation. Despite the fact that all ARBs have the same mechanism of action, their pharmacodynamic and pharmacokinetic profiles differ from one another. The ARBs can provide renoprotection in immunoglobulin A (IgA) and diabetic nephropathy, as well as beneficial haemodynamic and neurohormonal effects in heart failure.
	Neldam & Edwards (2009)	When used alone or in combination with other antihypertensive medications, telmisartan 80 mg/hydrochlorothiazide 25 mg (T80/H25) offers long-term and well-tolerated additive blood pressure management.
	Matsumori (2003)	The candesartan group had a slightly lower rate of confirmed CHF progression than the placebo group. Candesartan therapy was also associated with a lower risk of cardiovascular complications than placebo treatment. Hemodynamics improved significantly in the actively treated community. Candesartan was well received by the patients. When compared to placebo, candesartan cilexetil (8 mg/day) substantially slowed the progression of CHF.
Candesartan cilexetil	Israili (2000)	The antihypertensive efficacy of the ARBs is based on the regular mg dose: candesartan cilexetil > telmisartan = losartan > irbesartan = valsartan > eprosartan. Changes in pharmacokinetic parameters due to ageing, mild to moderate renal disease, and heart failure do not often necessitate dose modification; however, in patients with hepatic disease, dosage for eprosartan, losartan, telmisartan, and valsartan must be individually tailored. Except for the combination of digoxin and telmisartan, pharmacokinetic drug-drug interactions are uncommon. ARBs are a common treatment for hypertension because they are both safe and effective. The advantages of ARB therapy extend beyond blood pressure regulation. They can provide renoprotection in diabetic nephropathy and have

	beneficial haemodynamic and neurohormonal effects in heart failure.
Fukui et al. (2003)	The CASE-J study contrasts the effectiveness of candesartan, an angiotensin II receptor antagonist, and amlodipine, a third-generation calcium channel blocker, in preventing cardiovascular attacks and death from any cause. Over the last decade, there has been a lot of buzz about antihypertensive drugs' recently discovered ability to avoid cardiovascular events rather than just lower blood pressure. Based on a pathophysiological mechanism of action, angiotensin II receptor antagonists are likely to have benefits for ameliorating endothelial dysfunction and fostering vascular remodelling, as well as providing cardiac and renal safety. Calcium channel blockers and angiotensin II receptor antagonists have been shown to be effective in lowering blood pressure and are now widely used around the world. As a result, in many nations, even a slight difference in true endpoints, such as cardiovascular events and death, makes a big difference in terms of health burden and expense.
McInnes et al. (2000)	As antihypertensive agents, fixed combinations of candesartan cilexetil and hydrochlorothiazide 8/12.5 mg and lisinopril and hydrochlorothiazide 10/12.5 mg once daily are equally efficient. The set combination of candesartan and cilexetil is tolerated better than the one with lisinopril.

Table 4.3.2 (a). Dabigatran vs. rivaroxaban.

Included study	Dabigatran		Rivaroxaban	
	No. of patient with positive effect	Total subject	No. of patient with positive effect	Total subject
Alcusky et al. (2018)	39	201	64	173
Larock et al. (2014)	27	34	26	35
Villines et al. (2019)	12686	12763	12663	12763

Table 4.3.2 (b). Dabigatran vs. warfarin.

Included study	Dabigatran		Warfarin	
	No. of patient with positive effect	Total subject	No. of patient with positive effect	Total subject
Amin et al. (2019)	2414	4297	2363	4297
Amin et al. (2019) - 2	3436	18131	3510	18131
Deitelzweig et al. (2019)	6403	6698	6369	6698
Koretsune et al. (2019)	2488	2504	3068	3103
Nagao et al. (2015)	161	173	176	190
Olesen et al. (2014)	6762	7128	9399	9902
Stepanyan et al. (2014)	83	89	107	114
Winkle et al. (2014)	162	426	358	1113

Table 4.3.2 (c). Candesartan cilexetil vs. lisinopril and placebo.

Included study	Candesartan cilexetil		Lisinopril or placebo	
	No. of patient with positive effect	Total subject	No. of patient with positive effect	Total subject
Matsumori (2003)	11	148	32	144
McInnes et al. (2000)	129	237	72	116

4.4 Meta-analysis

Figure 4.4 (a) and (b) below, analyzed the positive effects of benzimidazole drug (dabigatran) and non-benzimidazole drugs (rivaroxaban and warfarin) towards the cardiovascular patients receiving the treatment. While, the analysis of the cardiovascular patients receiving the treatment that show the positive effects of other benzimidazole drug (candesartan cilexetil) and non-benzimidazole drugs (lisinopril and placebo) were shown in Figure 4.4 (c). The data analysis was presented in the form of forest plot of meta-analysis.

For Figure 4.4 (a), there were three studies comparing dabigatran and rivaroxaban. Out of the three studies, only one study by Alcusky et al. (2018) showed significant result. While the other two studies by Larock et al. (2014) and Villines et al. (2019) were not significant. However, the pooled result showed no significant results, indicating that more studies are needed to confirm this.

Next, for Figure 4.4 (b), there were eight studies comparing dabigatran and warfarin. Out of the eight studies, only one study by Winkle et al. (2014) showed significant result. While the other seven studies were not significant. However, the pooled result showed no significant results, indicating that more studies are needed to confirm this.

Meanwhile, for Figure 4.4 (c), there were only two studies comparing candesartan and non-benzimidazole (lisinopril and placebo). Out of the two studies, only one study by

Matsumori (2003) which compared candesartan and placebo showed significant result. While the other study by McInnes et al. (2000) that compared candesartan and lisinopril was not significant. However, the pooled result showed a significant result.

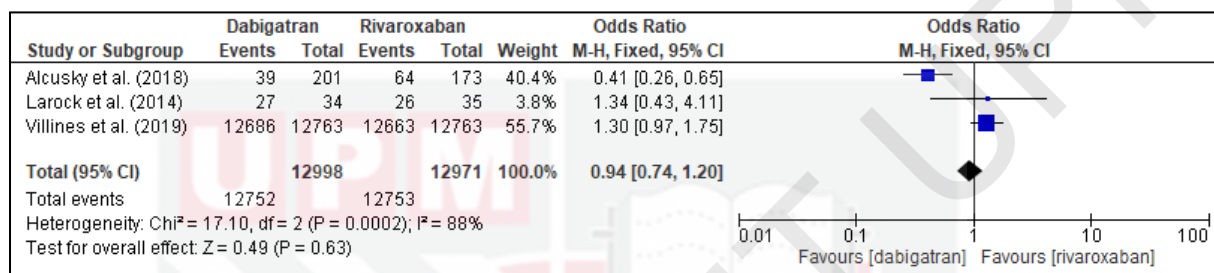


Figure 4.4 (a). Forest plot of the meta-analysis from three included studies on the effectiveness of the benzimidazole drug (dabigatran) as compared to non-benzimidazole drug (rivaroxaban) in treating cardiovascular conditions. $I^2 = 88\%$ indicates the presence of significant heterogeneity, and fixed effect model was used. The plot showed that dabigatran and rivaroxaban were not significantly different, with $p = 0.63$ at 95% CI.

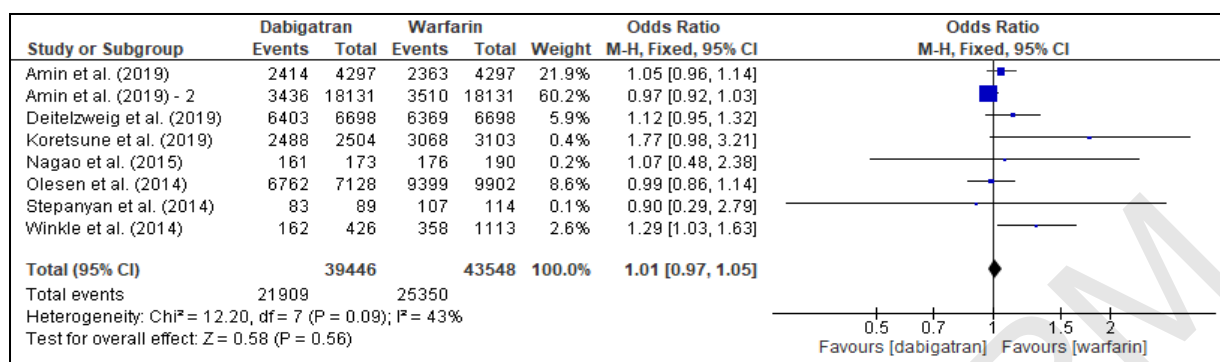


Figure 4.4 (b). Forest plot of the meta-analysis from eight included studies on the effectiveness of the benzimidazole drug (dabigatran) as compared to non-benzimidazole drug (warfarin) in treating cardiovascular conditions. $I^2 = 43\%$ indicates the presence of moderate-to-low heterogeneity, and fixed effect model was used. The plot showed that dabigatran and warfarin were not significantly different, with $p = 0.56$ at 95% CI.

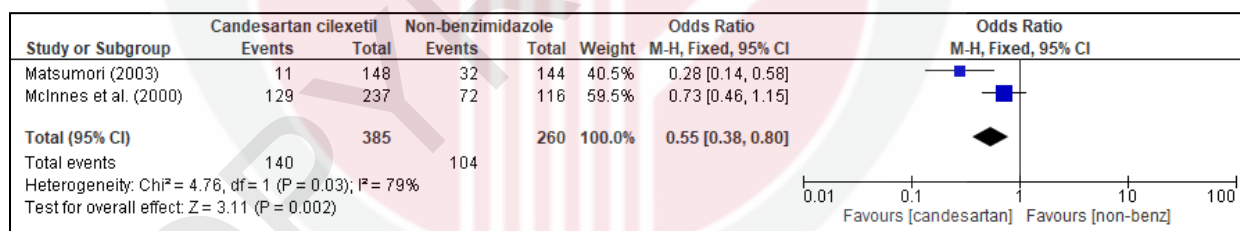


Figure 4.4 (c). Forest plot of the meta-analysis from two included studies on the effectiveness of the benzimidazole drug (candesartan cilexetil) as compared to non-benzimidazole drug (lisinopril) and placebo drug in treating cardiovascular conditions. $I^2 = 79\%$ indicates the presence of significant heterogeneity, and fixed effect model was used. The plot showed that candesartan cilexetil, lisinopril and placebo drug were significantly different, with $p = 0.002$ at 95% CI.

4.5 Quality Assessment

The quality assessment for all included studies were calculated in the form of percentage to determine the quality of the studies (either low or high) as shown in Table 4.5 (b). The interventional studies involved 14 items whereas the non-interventional studies only included 11 items. The calculation was done by referring to the data stated in Table 4.5 (a). The studies that show the percentage below than 50% is considered low quality, while the percentage above than 50%, are considered as high-quality studies.

Table 4.5 (a). Quality assessment for all included studies that were determined according to the guidelines from the Alberta Heritage Foundation for Medical Research (AHFMR) statement.

		Item 1 (No N/A)	Item 2 (No N/A)	Item 3	Item 4 (No N/A)	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13 (No N/A)	Item 14 (No N/A)
DRUGS	PAPER (author, year)	Question or objective is sufficiently described	Study design is evident and appropriate	Method of subject/com parison group selection or source of information is described and appropriate	Subject and comparison group character istics is sufficient ly described	If intervention al and random allocatio n was possible, is it described ?	If intervention al and blinding of investiga tors was possible, is it reported ?	If intervention al and blinding of subjects was possible, is it reported ?	Outcome and exposure measures is well defined and robust with bias measurement/ misclassification reported? means of assessment is reported?	Sample size appropriate	Analysis is described and appropriate	Estimate of variance is reported for the main results	Controlled for confounding	Results is reported in sufficient detail	Results support the conclusions
Dabigatran	Hu & Liu (2020)	2	2	1	2	N/A	N/A	N/A	2	2	2	0	0	2	2
	Akgullu et al. (2013)	2	2	2	2	N/A	N/A	N/A	1	1	2	1	2	1	1
	Arachchilage & Cohen (2013)	2	2	2	2	N/A	N/A	N/A	2	0	2	1	2	2	2
	Kasmeridis et al. (2013)	2	2	2	2	N/A	N/A	N/A	2	2	2	1	2	2	2
	Larock et al. (2014)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
	Nagao et al. (2015)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
	Olesen et al. (2014)	2	2	2	2	2	0	0	2	2	2	2	2	2	2

	Stepanyan et al. (2014)	2	2	2	2	N/A	N/A	N/A	2	2	2	1	2	2	2
	Winkle et al. (2014)	2	1	2	2	N/A	N/A	N/A	2	2	2	2	0	2	2
	Alcuskys et al. (2018)	2	2	2	2	N/A	N/A	N/A	2	2	2	0	2	2	2
	Amin et al. (2019)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
	Amin et al. (2019) - 2	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
	Beshir et al. (2017)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
	Chang et al. (2015)	2	1	1	1	N/A	N/A	N/A	1	2	1	0	1	1	1
	Deitelzweig et al. (2019)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
	Koretsune et al. (2019)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
	O'Brien et al. (2016)	1	2	2	2	N/A	N/A	N/A	2	2	2	0	2	2	2
	Rago et al. (2017)	2	1	0	2	N/A	N/A	N/A	2	2	2	1	2	2	2
	Villines et al. (2019)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2	2
Pimoben dan	Chu et al. (1995)	2	2	0	2	0	2	0	2	1	2	1	2	2	2

Telmisartan	Bajcetic et al. (2007)	2	2	2	2	2	0	2	2	2	2	2	2	2
	Chang et al. (2016)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	2
	Moon et al. (2019)	2	2	2	2	N/A	N/A	N/A	2	2	2	2	2	1
	Bohm et al. (2017)	2	2	2	2	N/A	N/A	N/A	2	2	2	1	2	2
	Israili (2000)	2	2	2	2	N/A	N/A	N/A	2	2	2	1	2	2
	Neldam & Edwards (2009)	2	2	2	2	2	2	2	2	2	2	2	2	2
Candesartan cilexetil	Matsumori (2003)	2	2	2	2	2	2	2	2	2	2	2	2	2
	Israili (2000)	2	2	2	2	N/A	N/A	N/A	2	2	2	1	2	2
	Fukui et al. (2003)	2	2	2	2	N/A	N/A	N/A	2	2	2	1	2	2
	McInnes et al. (2000)	2	2	2	2	2	2	2	2	2	2	2	2	2

Table 4.5 (b). Quality assessment calculation in the form of percentage.

Drugs	Included studies	Percentage Calculation		
		11 items (per 22)	14 items (per 28)	Percentage
Dabigatran	Hu & Liu (2020)	17	N/A	77.3%
	Akgullu et al. (2013)	17	N/A	77.3%
	Arachchillage & Cohen (2013)	19	N/A	86.4%
	Kasmeridis et al. (2013)	21	N/A	95.5%
	Larock et al. (2014)	22	N/A	100%
	Nagao et al. (2015)	22	N/A	100%
	Olesen et al. (2014)	N/A	24	85.7%
	Stepanyan et al. (2014)	21	N/A	95.5%
	Winkle et al. (2014)	19	N/A	86.4%
	Alcusky et al. (2018)	20	N/A	90.9%
	Amin et al. (2019)	22	N/A	100%
	Amin et al. (2019) - 2	22	N/A	100%
	Beshir et al. (2017)	22	N/A	100%
	Chang et al. (2015)	12	N/A	54.5%
	Deitelzweig et al. (2019)	22	N/A	100%
	Koretsune et al. (2019)	22	N/A	100%
	O'Brien et al. (2016)	19	N/A	86.4%
	Rago et al. (2017)	18	N/A	81.8%
	Villines et al. (2019)	22	N/A	100%
Pimobendan	Chu et al. (1995)	N/A	20	71.4%
Telmisartan	Bajcetic et al. (2007)	N/A	26	92.9%
	Chang et al. (2016)	22	N/A	100%
	Moon et al. (2019)	22	N/A	100%
	Bohm et al. (2017)	21	N/A	95.5%
	Israili (2000)	21	N/A	95.5%
	Neldam & Edwards (2009)	N/A	28	100%

	Matsumori (2003)	N/A	28	100%
Candesartan cilexetil	Israili (2000)	21	N/A	95.5%
	Fukui et al. (2003)	21	N/A	95.5%
	McInnes et al. (2000)	N/A	28	100%

N/A = not applicable



CHAPTER 5

DISCUSSION

The aim of this study is to determine how far the effectiveness of benzimidazole compound in the drug production for cardiovascular disease (CVD). This is because, in clinical studies, it is well said that molecules that having benzimidazole compound structure will exhibit promising application as well as in biological studies (Kamanna, 2019). Hence, through this study, it will compare the benzimidazole and non-benzimidazole susceptibility towards the patient with low, medium and high risk of cardiovascular condition.

5.1 Data Analysis

5.1.1 Study Population and Study Design

Referring to Table 4.2 (a), the study population were coming from diverse state of country including United States of America (USA), United Kingdom (UK), Japan, China, Germany, Italy and more. However, the majority of the country was where these benzimidazole compounds were reported in the US, especially for dabigatran. This is because the oral anticoagulant dabigatran was the first to be approved in the United States (Ganetsky et al., 2011). So, the primary research focus is on the comparative effectiveness and safety of new oral anticoagulants (or non-vitamin K antagonist oral anticoagulants), which is dabigatran (Lauffenburger et al., 2015). Furthermore, dabigatran etexilate is a reversible direct thrombin inhibitor that has been licenced for

stroke prevention in atrial fibrillation (SPAF) and primary venous thromboembolism prevention and therapy in the United States, Europe and India (Trailokya & Hiremath (2018).

Based on Table 4.2 (a) and Figure 4.2, there were many articles on the non-intervention studies with total of 24 studies as compared to only six interventional studies. The non-interventional studies were mostly conducted for cohort study that comprised of either prospective or retrospective. This is because, Gamble (2014) had mentioned that cohort studies are considered as feasible study design alternative to randomized controlled trial (RCTs), which have several drawbacks such as only need small sample size, high cost, and a rigid study methodology that is not always indicative for regular treatment. In addition to that, cohort studies may follow patients for long periods of time in relatively low cost, but not RCTs (Gamble, 2014). Furthermore, according to Thiese (2014), retrospective observational study designs are frequently used to investigate probable causation in exposure-outcome correlations and, as a result, influence preventive strategies. These common observational studies include cross-sectional, case-control, case-crossover, retrospective, and prospective cohorts. However, a systematic review suggested that more interventional studies are needed to assess the direct effects of therapy or disease prevention interventions specifically (Thiese, 2014). An example of the interventional study would be a research in which the participants are randomly assigned to receive either aspirin or a placebo for a set period of time to see if the treatment has an effect on the future risk of developing cerebrovascular events. That is why interventional study is important to represent the real effect of an intervention (Aggarwal & Ranganathan, 2019).

5.1.2 Benzimidazole Drug of Choice

According to Kamanna (2019), the increased interest in benzimidazole compounds is due to their excellent properties, which include greater stability, bioavailability, and substantial biological activity. The first benzimidazole developed and licenced for human use was thiabendazole in 1962, and more derivatives of benzimidazole have been clinically approved since then, including albendazole, mebendazole, and flubendazole as anthelmintics; omeprazole, lansoprazole, and pantoprazole as proton pump inhibitors; astemizole as antihistaminic; envirodin as antiviral; and candesartan cilexetil and telmisartan as antihypertensives. In biological and therapeutic research, molecules having benzimidazole motifs have showed promise. It is currently a favoured moiety with a variety of pharmacological properties, including the ability to inhibit a variety of enzymes engaged in a variety of therapeutic applications (Shingalapur et al., 2010).

5.1.2.1 Dabigatran

Dabigatran was the most popular benzimidazole drug that being studied in cardiovascular condition in comparison to pimobendan, telmisartan and candesartan. According to Iturbe-Hernandez (2020), for oral anticoagulation, dabigatran may be considered as a first-line option. It is believed to have a good efficacy and safety profile towards the patients.

5.1.2.1.1 Dabigatran vs. Warfarin

Dabigatran, a low-risk alternative to warfarin, is the most commonly prescribed medication (Olesen et al., 2014). When compared

to warfarin, NOACs were linked with decreased rates of stroke/SE and varied rates of MB in very old NVAF patients (Deitelzweig et al., 2019). While in Japanese patients with NVAF, dabigatran was linked to a decreased risk of stroke, systemic embolism, cerebral haemorrhage, and severe bleeding when compared to warfarin (Koretsune et al., 2019).

According to the study by Akgullu et al. (2013), in the RE-LY study, researchers discovered that dabigatran at a dose of 110 mg and warfarin caused thromboembolic events at identical rates for moderate risk patients. Higher doses (150 mg) of dabigatran, on the other hand, resulted in decreased incidence of thromboembolic events. In the same trial, it was discovered that twice-daily doses of 110 mg dabigatran resulted in less bleeding than warfarin. NOACs (direct thrombin inhibitors and direct factor Xa inhibitors) are a new oral anticoagulant that has recently been licenced for the prevention of atrial fibrillation (AF)-related thromboembolism. Dabigatran 150 mg twice daily, for example, prevented ischemic stroke. Kasmeridis et al. (2013) added up by saying that, only if the new drugs are utilised properly will they be effective, safe, and cost-effective. Uninterrupted dabigatran therapy in catheter ablation (CA) for AF appears to be a safe and effective anticoagulant therapy that is similar to continuous warfarin; nevertheless, when using dabigatran during CA, it is critical to pay strict attention to the APTT values (Nagao et al., 2015). This was also supported by Rago et al. (2017) mentioned that dabigatran etexilate, a direct thrombin inhibitor, was the first new generation oral anticoagulant to emerge as a potential

replacement for warfarin in the prevention of arterial TE in patients with AF.

In high-risk cases, Hu & Liu (2020) had mentioned that warfarin is far less effective than dabigatran at preventing new thromboses in arteries in high-risk patients. Dabigatran is an alternative to warfarin as the preferred orally administered anticoagulant (“blood thinner”) in some circumstances since it does not require frequent blood tests for international normalised ratio (INR) monitoring while providing equal efficacy results. To support this, another study by Arachchillage & Cohen (2013) concluded that, warfarin has a narrow therapeutic range, slow onset/offset of action, inconsistent response, regular laboratory testing, and various interactions with food, medications, and alcohol limit warfarin's use. Because they do not require routine anticoagulant monitoring, thus new oral anticoagulants (NOAC) have the potential to be a substantial advancement.

5.1.2.1.2 Dabigatran vs. Warfarin and Rivaroxaban

In general, individuals who are started on rivaroxaban or apixaban have a higher risk of stroke and bleeding than those who start on warfarin or dabigatran (Olesen et al., 2014). When compared to warfarin, all DOACs showed a decreased risk of MACE. Amin et al.

(2019), mentioned that when compared to warfarin, DOACs were linked with a lower to similar risk of stroke/SE and MACE in the senior Medicare population with NVAF, but with varied comparative risks for MB and net clinical outcome (NCO). In this trial, dabigatran was linked with a considerably lower major bleeding risk than rivaroxaban among NVAF patients who were newly started on standard-dose DOAC medication, but no significant difference in stroke risk (Villines et al., 2019).

According to Stepanyan et al. (2014), in this group of AF patients having CA, peri-procedure dabigatran or rivaroxaban did not result in an increase in bleeding or thromboembolic (TE) events when compared to continuous warfarin. Apixaban use was linked to a lower rate of stroke/systemic embolism (SE), major bleeding (MB), and major adverse cardiac events (MACE) when compared to warfarin; dabigatran was linked to a lower rate of MACE; and rivaroxaban was linked to a lower rate of stroke/SE, MACE, and MB but a higher rate of MB (Amin et al., 2019). In patients with NVAF, incorrect use of dabigatran and rivaroxaban is common and may result in adverse effects (AEs). As a result, Larock et al. (2014) suggested that it is necessary to reinforce health-care providers' and patients' education.

5.1.2.2 Pimobendan

According to Kato (1997), pimobendan is a benzimidazole-pyridazinone derivative that has both inotropic and vasodilatory effects. There were a number of clinical investigations have shown that a single oral or intravenous dose of pimobendan improves left and right ventricular performance in congestive heart failure patients. Additionally, pimobendan has also been proven to be useful as an add-on treatment in patients with moderate-to-severe chronic heart failure who are on diuretic and digitalis medication, with or without vasodilator medication. In the same study, he also mentioned that pimobendan, a novel cardiotonic vasodilator, was well-tolerated and provided the maximal efficacy in acute and chronic heart failure patients.

Herein, the summary of this systematic review on pimobendan. For moderate risk, overall, pimobendan improves systolic function by increasing contraction efficiency, reducing the arrhythmogenic side effects of other positive inotropes whose main mechanism of action is to elevate myocardial intracellular calcium (Gordon & Kittleson, 2008). For example, the end-systolic dimension of the left ventricle, systolic blood pressure, and diastolic blood pressure all fell by 8 to 11 percent. For more than 8 hours, 5 milligrammes (mg) of pimobendan improved cardiac function (Chu et al., 1995).

5.1.2.3 Telmisartan

Angiotensin II receptor blockers (ARBs) are extremely efficient antihypertensive drugs which have tolerability properties that are comparable to placebo. Telmisartan, with a half-life of roughly 24 hours, is the longest of the commercially available ARBs. This shows that telmisartan's activity lasts a long time in order to maintain blood pressure control during the once-daily dosage interval (Gosse, 2006). According to Sharpe et al. (2001), they concluded that telmisartan was well tolerated in patients with mild to moderate hypertension, and it was found to be less likely than lisinopril (non-benzimidazole compound) to elicit a symptom like persistent, dry cough.

The summary of this systematic review, include the findings from Bajcetic et al. (2007) study. They strongly imply that simultaneous treatment with nisoldipine improves telmisartan bioavailability in hypertensive patients with a moderate risk. Through the PPAR/STAT3 pathway, Chang et al. (2016) stated that telmisartan reduced hyperglycemia-induced heart fibrosis. Angiotensin II receptor blockers (ARBs) are a relatively recent class of orally active antihypertensive drugs that are both effective and well tolerated. The ARBs may provide renoprotection in immunoglobulin A (IgA) and diabetic nephropathy, as well as favourable haemodynamic and neurohormonal effects in heart failure (Israili, 2000).

Furthermore, given alone or as part of a multi-antihypertensive regimen, telmisartan 80 mg/hydrochlorothiazide 25 mg (T80/H25) provides sustained and well-tolerated additive BP control for high-risk patients (Neldam & Edwards, 2009). Treatment-induced very low blood pressure was linked to an elevated risk of numerous cardiovascular disease events. Bohm et al. (2017) summarized that although it is impossible to rule out the possibility of reverse causality, these findings show that the lowest blood pressure achievable is not always the best objective for high-risk patients.

5.1.2.4 Candesartan

Candesartan cilexetil is well tolerated in patients with hypertension. In study by McClellan and Goa (1998), they supported that patient with mild to severe essential hypertension, oral candesartan cilexetil 8 to 32mg decrease blood pressure dose-dependently and efficiently when given once day. Blocking the renin–angiotensin–aldosterone system (RAAS) is an essential therapeutic technique for reducing the progression of cardiovascular risk factors to established cardiovascular illnesses. Angiotensin receptor blockers (ARBs) have emerged as effective and well-tolerated alternatives to an angiotensin-converting enzyme inhibitor (ACEi) in the treatment of RAAS blockage in recent years. Candesartan, an ARB, was first discovered to be an effective once-daily antihypertensive therapy (Meredith, 2007).

In this systematic review/meta-analysis, candesartan was compared to placebo for low risk. The candesartan group had a considerably lower rate of verified CHF progression than the placebo group. Candesartan medication was also associated with a decreased risk of cardiovascular events than placebo treatment. Hence, candesartan was well tolerated by the patients. In addition to that, in study by Matsumori (2003), mentioned that when compared to placebo, candesartan cilexetil (8 mg/day) significantly slowed the course of CHF.

In conjunction to that, candesartan was compared to lisinopril for intermediate risk. As antihypertensive medications, fixed combinations of candesartan cilexetil and hydrochlorothiazide 8/12.5 mg and lisinopril and hydrochlorothiazide 10/12.5 mg once day are equally effective. The fixed combination with candesartan and cilexetil is tolerated better than the one with lisinopril (McInnes et al., 2000). Another trial comparing candesartan and telmisartan for moderate risk by Israili (2000). The antihypertensive potency of the ARBs is based on the daily mg dose: candesartan cilexetil > telmisartan = losartan > irbesartan = valsartan > eprosartan. ARBs are a popular treatment for hypertension because they are both safe and effective. The advantages of ARB medication extend beyond blood pressure control. They may give renoprotection in diabetic nephropathy and may have positive haemodynamic and neurohormonal effects in heart failure.

Meanwhile, candesartan was compared to amlodipine in high-risk patients. According to Fukui et al. (2003), the CASE-J study compares the

effectiveness of candesartan, an angiotensin II receptor blocker, and amlodipine, a third-generation calcium channel blocker, in avoiding cardiovascular events and all-cause death. Based on a pathophysiological mechanism of action, angiotensin II receptor blockers (ARB) are likely to have advantages for ameliorating endothelial dysfunction and encouraging vascular remodelling, as well as giving cardiac and renal protection. Calcium channel blockers and angiotensin II receptor antagonists have been demonstrated to be helpful in lowering blood pressure and are now routinely used around the world.

5.1.3 Meta-Analysis

The meta-analysis has been conducted to get a clearer picture for the comparison between benzimidazole and non-benzimidazole drugs in contributing to CVD. The forest plot from the meta-analysis could provide a good explanation to support the effectiveness for benzimidazole drug in comparison to non-benzimidazole drug.

5.1.3.1 Dabigatran vs. Warfarin

As shown in Figure 4.4 (b), there were eight studies being compared to observe the effectiveness between dabigatran as benzimidazole drug with warfarin as non-benzimidazole drug in managing CVD patients. From the forest plot, it was shown that the effectiveness of both drugs dabigatran and warfarin were seemed to be equal. The plot showed that dabigatran and warfarin were

not significantly different to each other as anticoagulant drugs for CVD. They shared similar outcome towards CVD patients.

Nevertheless, one study examined that dabigatran has an advantage over warfarin in that it does not require constant monitoring of laboratory parameters or vitamin K ingestion. Dabigatran is so practical and user-friendly that it catches the attention of doctors looking for the greatest and most pleasant treatment options for their patients (Akgullu et al., 2013). Warfarin, the traditional anticoagulant, is ineffective at preventing new thromboses in arteries, but dabigatran is far more effective. Dabigatran is also being studied for a variety of clinical indications, and in some cases, it may be a better alternative to warfarin as the preferred orally administered anticoagulant (“blood thinner”) because it does not require frequent blood tests for INR monitoring while providing similar efficacy (Hu & Liu, 2020).

Furthermore, a systematic review by Miller et al. (2012), concluded that in individuals with atrial fibrillation (AF), the new oral anticoagulants (dabigatran) are more effective than warfarin at preventing stroke and systemic embolism. They appear to have a favourable safety profile, with a lower risk of cerebral bleeding, making those potential alternatives to warfarin.

5.1.3.2 Dabigatran vs. Rivaroxaban

As shown in Figure 4.4 (a), there were three studies being compared to observe the effectiveness between dabigatran as benzimidazole drug with rivaroxaban as non-benzimidazole drug in managing CVD patients. From the forest plot, it was shown that dabigatran and rivaroxaban was not significantly different to each other as anticoagulant drugs for CVD. This is because, less studies were been conducted to show their significant differences. As for now, this comparison remains unclear whether dabigatran is superior to rivaroxaban in CVD patients.

However, according to study by (Bai et al., 2017), rivaroxaban was as effective as dabigatran but better than warfarin in preventing ischemic stroke and systemic thromboembolism in patients with atrial fibrillation. And from the same study, they reported that the risk of major bleeding, as well as all-cause mortality and gastrointestinal bleeding, was considerably higher with rivaroxaban than with dabigatran.

Meanwhile, study by (Villines et al., 2019), they mentioned that compared to rivaroxaban, patients who started dabigatran had a decreased risk of severe bleeding. In addition, (Olesen et al., 2014) also mentioned the same thing where rivaroxaban users have a higher risk of stroke and bleeding than dabigatran users. Hence, dabigatran and rivaroxaban appear to have similar effectiveness, but rivaroxaban may be associated with an elevated bleeding risk.

5.1.3.3 Candesartan vs. Non-Benzimidazole

As shown in Figure 4.4 (c), there were only two studies being compared to observe the effectiveness between dabigatran as benzimidazole drug with lisinopril and placebo as non-benzimidazole drug in managing CVD patients. From the forest plot, it was shown that the effectiveness of both drugs candesartan and non-benzimidazole compound which consist of lisinopril and placebo were significantly different. Hence, here it could say that candesartan is better than the other in overall result. But, only one study which is placebo was significant, but the other one with lisinopril was not. So still, candesartan could not show clear comparison with lisinopril. More studies are needed here.

So, for lisinopril, in the comparison with candesartan, study by McInnes et al. (2000) reported that both medications were well tolerated but the proportion of patients with at least one adverse event was considerably larger in the lisinopril group. And the proportion of patients terminating therapy due to adverse events was greater in the lisinopril group compared with the candesartan cilexetil group. While for the placebo, in the comparison with candesartan, both medication was significantly different as candesartan was well tolerated by referring to study by Matsumori (2003). Furthermore, candesartan medication was associated with a decreased risk of cardiovascular events than placebo treatment.

5.1.4 Quality Assessment

According to Table 4.5 (b), the given percentage demonstrates that all of the research included in this systematic review/meta-analysis were made up of high-quality, with the percentage of above 50%. This quality assessment was successful have been done to reduce the risk of bias for this systematic review/meta-analysis.

5.2 Limitation

In comparison to dabigatran, there were fewer research on pimobendan, telmisartan, and candesartan cilexetil as benzimidazole compounds in the management of CVD patients. In contributory CVD patients, pimobendan, telmisartan, and candesartan cilexetil have antihypertensive mechanisms of action. This indicates that benzimidazole chemical derivatives that operate as antihypertensive as well as anticoagulant are the subject of less studies. Despite the fact that telmisartan and candesartan had less articles than dabigatran, pimobendan had the smallest number of papers, with only one item for this study. This demonstrates that pimobendan was insufficient to support this investigation. Furthermore, less study on intervention being done for all drugs stated in this study.

Apart from that, this research only looked at anticoagulant and antihypertensive drugs. Because CVD is such a broad disease that it can be further subdivided into various types, there are apparently a lot of mechanisms of action for medications used to manage it. CVD is defined as a condition that affects the heart and blood vessels. However, this research was limited to mechanisms that occur in blood vessels. As a result, it was narrowed

down to two types of CVD pharmacological agents: anticoagulant and antihypertensive. Meta-analysis is not possible due to a lack of data. The numerical value needed to do the meta-analysis is not provided in all studies. Telmisartan and pimobendan, in particular. Unlike dabigatran and candesartan cilexetil, neither of these medicines has undergone any type of meta-analysis.

5.3 Future Study

To overcome the limitation present in this study, more research on pimobendan, telmisartan and candesartan cilexetil as antihypertensive agents for CVD are needed, provided with more interventional studies. This is important because in interventional studies, on the other hand, the researcher intentionally interferes with nature by executing an intervention on some or all study participants to see how the intervention affects the natural sequence of events, in this case, to see the effectiveness of the drug compound in more accurate outcome (Aggarwal & Ranganathan, 2019). In conjunction to that, it is a need to add more other mechanism of CVD agents to be studied other than anticoagulant and antihypertensives to reduce bias of study. Other than that, more sufficient data should be adequately provided to do meta-analysis for other drugs like telmisartan and pimobendan. According to Kamanna (2019), he mentioned that the lack of a comprehensive collection of various research articles in each activity capable of providing insight into the compounds' SAR (structure activity relationship) study is most likely to blame. Thus, more studies on this compound should be made as the biological characteristics of these new generations of benzimidazoles would be a useful matrix for developing better therapeutic agents in the future.

CHAPTER 6

CONCLUSION

This study aimed to study the effectiveness of benzimidazole drug compound on CVD patients by comparing it to non-benzimidazole compound. So, out of 1033 articles, only 29 were selected as included studies. In this study, benzimidazole-derived compounds have demonstrated potential as anticoagulant as well as antihypertensive agents in managing cardiovascular condition of patients. The use of each drug compound, dabigatran, pimobendan, telmisartan and candesartan, had appealing their mechanisms of action in combating the cardiovascular conditions.

In conclusion, from the systematic review, benzimidazole derivatives compound that consist of dabigatran, pimobendan, telmisartan and candesartan were shown a good potential as an alternative medicine in treating CVD as compared to the other compounds. However, after run for meta-analysis, benzimidazole compound could not show a better outcome in managing CVD, so they possess the same positive effect as well as non-benzimidazole. Only benzimidazole compound of dabigatran and candesartan were further undergone the meta-analysis as they have values to be evaluated. While, the other two compounds, which are pimobendan and telmisartan could not provide enough studies for meta-analysis. Hence, more studies on benzimidazole derivatives should be made as the biological characteristics of these new generations of medicines would be a useful matrix for developing better therapeutic agents in the future.

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