Antihypertensive Drugs and Risk of Cancer: A Pharmacovigilance Study

A project submitted
by
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This work is dedicated to my parents and siblings for their love and constant support…

Certification Statement

This is to certify that this project titled “Antihypertensive Drugs and Risk of Cancer: A Pharmacovigilance Study” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Dr. Md. Mesbah Uddin Talukder, Associate Professor, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed by,

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Countersigned by the supervisor

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Abstract

Antihypertensive drugs are widely used for the treatment of hypertension, heart failure and, recently, for cardiovascular risk reduction. Experimental studies implicate antihypertensive drugs in the regulation of cell proliferation, tumor progression and even cancer. The purpose of this study is to assess the association between cancer and previous use of antihypertensive medication, taking into account the class of antihypertensive drug and the occurrence of cancer between male and female. I took data of the signal from WHO Global Pharmacovigilance database named VigiBase and this database is available for general people by a web application VigiAccess. I use PRR and chi-square method to determine conduct my study. We select some antihypertensive drugs of several classes. This pharmacovigilance study suggests that all antihypertensive drugs are not associated with cancer. But some specific drugs of antihypertensive drugs which has large amount of reports has the risk of this association.

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List of abbreviations

ADR: Adverse Drug Reaction

WHO: World Health Organization

CIOMS: The Council for International Organizations of Medical Sciences

PRR: Proportional Reporting Ratio

ACE: Angiotensin Converting Enzyme

BP: Blood Pressure

CCBs: Calcium Channel Blockers

ARBs: Angiotensin II receptor blockers

UV: Ultraviolet

LDL: Low Density Lipoprotein

HDL: High Density Lipoprotein

RCC: Renal Cell carcinoma

PC: Prostate cancer

TGA: Therapeutic Goods Administration

MHRA: Medicines & Healthcare Products Regulatory Agency

CHAPTER ONE

INTRODUCTION

Chapter 1: Introduction

1.1 Relationship between antihypertensive drugs and cancer

To begin with, the debate about the association between antihypertensive drugs and cancer has been going on for decades. In 1975, at first, an article published which proved that there is a relationship between high blood pressure and cancer (Hedner, Narkiewicz, Kjeldsen, & Oparil, 2011; Pero et al., 2007). Every year around 7.5 million of people die only for hypertension. Hypertension is known as silent killer due to its asymptomatic nature because it shows its dangerous effect before people can realize about it. People who are unable to manage hypertension further develop cardiovascular disease, problems in lung and kidney and even stroke (Kim & Andrade, 2016). Before 1960s, people who have hypertension were frequently treated just only while it is symptomatic but awareness was not that much in the time of treatment (Roberts, Stickley, Balabanova, & McKee, 2012). Among all 10 cases of hypertension 9 cases are unknown. There are several types of drugs used for the lowering of blood pressure. These drugs are not act on cause but on effect and the treatment for the hypertension is continued for a long period of time. It is thought that hypertension is a result of genetic trait but the reason is varies person to person around 30 to 50% according to their lifestyle, diet and environmental factor and this will increase with age (Kapil & Lobo, 2014). Sometimes cardiovascular disease known as the aggregation of disease which affects our circulatory system includes artery to capillary, kidney and even our lung (Johar & Bernstein, 2017). According to WHO, every year 17.5 million people are dying due to cardiovascular disease specially stroke as well as heart attack and by 2030 these number will increase higher than 23.6 million (Miremadi, Sherkat, & Stojanovska, 2016). Hypertension is responsible for heart disease, stroke, cancer and it is found that hypertension is the reason of death for heart disease which is approximately 45%, for stroke this rate is 51% and the rate is unknown for cancer. In developing countries around 29.6% of male and 34% of female can control their blood pressure among all people. In case of developed country this ratio is around 33.2% and 38.4 % respectably for male and female. WHO points out significance of essential services against HT as well as it pointed that wellbeing experts, particularly nurses, to create awareness among the general public individuals and they ought to take dynamic part in sorting out instructive gatherings against risk factors (Kilic, Uzunçakmak, & Ede, 2016). So, it is also necessary for the

patient of hypertension to take antihypertensive drugs. Every drug has some ADR and for antihypertensive drugs cancer is one of the ADR (Kato et al., 2015). Solid tumors like abnormally developed created tissues are made out of many sorts of cells including neoplastic, supporting vascular and inflammatory cells and fibroblasts. The greater part of cells in mass tumors has restricted self-renewal capacity and is non-tumorigenic. Just a little subpopulation has the capacity to renew and development of tumor broad self-recharge and tumor development. This little population is known as cancer stem cells. The idea of cancer first evolved from cancer stem cells around 150 years back which were outlined by Huntly and Gilliland in 1855 (Han, Shi, Gong, Zhang, & Sun, 2013). Contrasted with ordinary cells, cancer cells show expanded glucose digestion system and in addition changes in mitochondrial oxidative digestion system that are accepted to be the aftereffect of ceaseless metabolic oxidative anxiety. Most of the treatments for cancer are intended to exploit the metabolic and physiological contrasts that exist between cancer and ordinary cells.(Allen et al., 2014) ADRs are one of the main reasons for the occurrence of mortality as well as morbidity. Institute of Medicine in US reported, "Between 44,000 and 98,000 deaths occur annually from medical errors. Of this total, an estimated 7000 deaths occur due to ADRs." This report said that ADR is one of the leading reasons for the occurrence of death and increase the cost of healthcare system and the productivity of people. In Sweden 3 study has been done among the Swedish population and reported that the percentage of death is 3% among the people due to ADR which place in the 7^{th} position for the occurrence of death (Mouton et al., 2015). Nowadays the report of these ADRs are collected by several organizations, like WHO, from all over the world and stored in databases for further analysis. Again this assessing task for the analysis of data needs high effort and performed manually (Koutkias & Jaulent, 2016). A standout amongst the most essential aspects for the checking of drugs which are already in the market is the identification as well as examination of new drug, known as signals that may influence the utilization of a drug. Signal detection can be defined from CIOMS (The Council for International Organizations of Medical Sciences) Group VIII "Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or a set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" (Lerch, Nowicki, Manlik, & Wirsching, 2015). The objective for the detection of signal is to recognize new possibly causal associations, or new parts of

known associations. Conventional techniques for signal detection incorporate the audit of scientific writing, ICSRs, cases including "record cases", the survey of cases, Periodically Updated Reports, Periodic Benefit–Risk Evaluation Reports, Development Safety Update Reports, Annually updated Safety Reports, and Periodic ADR Reports etc. To support and upgrade the conventional strategies, statistical signal detection is used. At present for the detection of signal for ADR from the spontaneous reporting database some quantitative methods like Bayesian techniques, PRR, ROR etc. are used. Another quantitative process is SSA for the detection of ADR (I, Pratt, Kalisch, & Roughead, 2014). At present, Excess number of ADRs are observed which are coming from all over the world, published in different publications, newspaper develop burden for individuals working with drugs or patients to stay up to date with this improvement (Beckmann et al., 2014)(Beckmann et al., 2014). To put it plainly, the genuine practice for the detection of signal and administration needs to oversee two of the potentially conflicting objectives: (1) quality: distinguish every single genuine signal as right on time as could be expected under the circumstances, and (2) workload: let wellbeing specialists concentrate their valuable time on the assessment of genuine signal by lessening the quantity of false-positive signs and in this manner the work expected to survey them (Lerch et al., 2015). The result of signal detection is the adverse effect of drugs which come from all over the world and every year cancer is reported as adverse drug reaction against some antihypertensive drugs.

1.2 Types of antihypertensive drugs that can cause cancer

Antihypertensive drugs have carcinogenic potential which is a topic of debate since around 50 years (Gomez-Acebo et al., 2016). As an initial therapy different types of antihypertensive drugs are used to control the blood pressure effectively. By regulating the electrolyte balance as well as blood pressure hypertension can be treated. For the significant reduction of hypertension and its associated morbidity as well as mortality these drugs are effectively worked. To control the blood pressure effectively patients require combination of drugs maximum time at least two or more drugs which may lead to several adverse effect. The most common type of antihypertensive drugs are vasodilator, ACE inhibitor, diuretics, adrenergic blockers, angiotensin II receptor blockers, calcium channel blockers, beta blockers and alpha blockers. Thiazide diuretic is used as the treatment of first line for people who has high BP. (Arroll, Kenealy, & Elley, 2008) Many study said that diuretics and calcium channel blocker are mainly

responsible for cancer but according to the report on VigiAccess almost all types of antihypertensive drugs can cause cancer (A. M. Lindgren, Nissinen, Tuomilehto, & Pukkala, 2005). Angiotensin II receptor blocker has the ability to increase the risk of cancer (Olin, Veverka, & Nuzum, 2011). But the excess risk was found for those who were using antihypertensive drugs for more than 5 years.

1.2.1 ACE inhibitors

In the treatment of heart failure, management of renal insufficiency is really important to reduce the mortality rate and ACE inhibitors are most commonly used therapeutic agent in this case. To reduce the mortality rate due to heart failure ACE inhibitors is a standard medication which is proved by major studies. Their ideal hemodynamic change incorporates decrease of heart preload, afterload and systolic ventricular divider push bringing about expanded cardiovascular yield without proportionate increment in oxygen utilization. This hemodynamic modification keeps up glomerular filtration by enhancing the renal perfusion and advancing sodium discharge. Consequently they are instrumental in long haul administration of patients with hypertension, CHF, diabetic and non-diabetic nephropathy giving mortality advantage. But again the possibility of adverse drug reactions is high among these patients among one of them is cancer. Some study said that ACE inhibitors reduce the risk of cancer among patients but when other study done to prove this evidence they failed which means ACE inhibitors do not reduce the risk of cancer.

1.2.2 Beta blockers

In the management of heart failure and reduce the mortality rate beta blocker is useful. In case of young patient, the first line drug for hypertension is beta blocker (Ong, 2007). In the treatment of hypertension beta blocker are used increasingly and their action is almost like diuretics on heart disease and stroke. In recent years this drug has found to be a risk of cancer in increased amount. A case control study among Australia proved undoubtedly about the occurrence of kidney cancer and pelvic cancer people who use beta blocker.

1.2.3 Calcium channel blocker

Calcium channel blocker is one of the common types of antihypertensive drugs which used since 2 decades to treat the hypertension. Some researchers raise a question by

doubting that these drugs are responsible for heart attack. They essentially act by blocking calcium convergence through the voltage-gated calcium channel of cell layers of vascular smooth muscle. Recently some study said about the association between these agents and malignancy. For the treatment of hypertension CCBs are widely prescribed as an antihypertensive drug and also in the treatment of coronary heart disease. It has been guessed that calcium channel blockers (CCBs) may build tumor hazard, in light of the fact that their bar of calcium channels can hinder apoptosis and, along these lines encourage, the division of harmed cells with dangerous potential.

1.2.4 Diuretics

In medicine, diuretics are used to treat heart failure, hypertension, water poisoning, and certain kidney diseases etc. The antihypertensive actions of some diuretics (thiazides and loop diuretics in particular) are independent of their diuretic effect. That is, the reduction in blood pressure is not due to decreased blood volume resulting from increased urine production, but occurs through other mechanisms and at lower doses than that required to produce diuresis. Many studies are done to prove about the relationship between the use of diuretics and risk of cancer. Study proved that long term use of diuretics is responsible for renal cell carcinoma. (Wong-Ho Chow, 1995) A diuretic especially thiazide diuretics is used for the primary treatment of cancer and it has the ability to increase the risk of several carcinomas (Keith T. Flaherty1, 2005).

1.2.5 Angiotensin II receptor blockers

Angiotensin II receptor blockers are the primarily given successful drugs for hypertension patients and patients who are intolerance with this inhibitors will get benefit in several heart disease for example stable coronary heart disease . The tolerability is proven good and effective in case of Angiotensin II receptor blockers and around 25% of patients suffering from hypertension are taking this drug worldwide. Angiotensin-receptor blockers (ARBs) are used widely as an antihypertensive drug and at first approved in 1995 for clinical purpose. Losartan is the first discovered drug as ARBs. Several meta-analysis was done to determine the association of antihypertensive drugs and cancer which reported about the highly risk for the occurrence of cancer. But the mechanism for this type of association is still unknown.

1.2.6 Other antihypertensive drugs

By using plant extract or the products which are plant derived is useful for the treatment of hypertension. Many evaluations including invitro and invivo examinations prove that for the treatment of hypertension alkaloids is essential and it have the ability to prevent cardiovascular diseases (Bai, Wu, & Xu, 2015). In past, rauwolfia alkaloids for example Rauwolfia *serpentine* used commonly as hypertension treatment and it was thought to be the effective and safe drug in the treatment of hypertension. But now it was proved to have the ability to increase the risk of breast cancer among women. Methyldopa which is another antihypertensive drug is proved to have the carcinogenesis property.

1.3 Types of cancer due to using antihypertensive drugs:

Different types of cancer like Prostate cancer, breast cancer, colon cancer, throat cancer, renal cancer, skin cancer can occur due to using antihypertensive drugs though the number is moderately high but there is possibility to occur. Again long term use of antihypertensive drugs can cause cancer. For example, long-term use of ARBs and diuretic can cause skin cancer (Schmidt, Schmidt, Mehnert, Lemeshow, & Sorensen, 2015).

1.3.1 Skin cancer

Worldwide the number of cases for skin cancer is increasing due to the exposure of ultraviolet radiation on the skin. Skin is the cells in which the arrangement is integrated, complex that control several function and this functions are done by different layers of skin. Among all layers dermis is one and the thickness of the skin is depending on this layer. This thickness is different for men and women. The thickness is lower in women comparing with men and this thickness is begin to decrease after the age of 45 and aftereffect of menopause this decrease 10 % thinner. So, the absorption of UV light is higher in women than men due to the thickness of skin of women. Among all types of skin cancer basal cell carcinoma is most common. Other common types of skin cancer are squamous cell skin carcinoma and malignant melanoma. In case of basal cell carcinoma, around 8 skin cancer patient out of 10 have basal cell carcinoma. This type of skin cancer has a tendency to develop gradually and occurred due to UV radiation. If it left untreated, it can develop into adjacent ranges and attack the bone or different tissues underneath the skin. Again, around 2 cancer patients out of 10 are affected from

squamous cell skin carcinoma. These are generally showed up on sun-exposed zones of the body. Malignant melanoma is another type of cancer that can be developed from the melanocytes and melanocytes are the cell which contains pigment. Ultraviolet radiation is the primary reason for the occurrence of melanoma. The source of this ultraviolet radiation can be sun or tanning devices (Schmidt et al., 2015). The International Agency for Research on Cancer finds, ‘’tanning beds are carcinogenic to humans and that people who begin using tanning devices before age 30 are 75% more likely to develop melanoma.’’ Worldwide the main cause of skin cancer is exposure of UV radiation on skin and some antihypertensive drugs have the potential to cause carcinogen as they have the ability to absorb UV radiation directly from sun thus act as photosensitizing agent.

1.3.2 Breast cancer

Among all dangerous as well as fatal diseases cancer is one and nowadays the most common cancer among all women is breast cancer. Due to breast cancer the mortality rate among women is increasing and antihypertensive drugs has the ability to cause cancer (Yu & Wang, 2016). Cancer stem cells are present inside stem cell which has the ability to self-renew and to bring about the heterogeneous heredities of malignancy cells that contain tumors. Among some type of cancer like breast cancer CSCs are found to be present and adiponectin may involve with the progression of cancer cells. Adipose tissue is responsible for the synthesis and secretion of adiponectin. Increase production of adiponectin may involve in the occurrence of breast cancer. Antihypertensive drugs supposed to decrease this amount of production but some antihypertensive drugs do not decrease this production for example metoprolol. As per the past information, a few antihypertensive regimens increment the plasma adiponectin levels (Liu et al., 2016). In case of metoprolol, Study show that plasma concentrations of adeponectin do not change but increase the LDL cholesterol which may lead to breast cancer (Yilmaz et al., 2007). Several factors that are related with breast cancer can be genetic as well as alcohol consumption, diet, lifestyle are responsible for breast cancer (Shareef, Ashraf, & Sarfraz, 2016). The result is inconsistent when studies were done to find out the association between drugs for hypertension treatment and breast cancer. A diuretic which is a class antihypertensive agent show that this agents has the ability for the occurrence of breast cancer. Again calcium channel blockers has also the potential to occur breast cancer because both of this drugs can inhibit the cell apoptosis process aftereffect influence the

synthesis and metabolism of insulin. Some cases show about the association between antihypertensive drugs and breast cancer but while some are not. Due to change the formulation of drugs like sustained release or immediate release the risk of this type of occurrence increase (Babette S. Saltzman, 2013). some study said about the inhibition of apoptosis due to using antihypertensive agents thus some show that this can facilitate cell division with the potential of malignant which increase the risk associated with breast cancer.

1.3.3 Renal cell carcinoma

Any type of cancer that has the formation in the tissue part of kidney and renal cell carcinoma is most common (Richardson & Hamra, 2010). The yearly mortality-to-rate proportion with RCC is fundamentally higher contrasted with other urological malignancies, and its occurrence has been expanding consistently in late decade. Renal cell disease is a generally irregular tumor. Every year worldwide the patient diagnosed due to renal cell cancer is around 200000 (Waxman, Kenny, & Ngan, 2008). Renal cell carcinoma (RCC) emerges essentially in the renal parenchyma and records for more than 90% of kidney carcinomas. RCC has the most elevated death rate among genitourinary growths and its occurrence has risen consistently, with a worldwide rate of around 200000 new cases and a death rate of more than 100000 patients yearly (Lv et al., 2014). For the progression of different type of cancer adiponectin which is a type of cytokine released from adipose tissue, take an important place. Late reviews have shown that low serum and plasma adiponectin levels in patients with RCC are related with a forceful phenotype and metastasis. Moreover, preclinical reviews have exhibited that exogenous adiponectin is fit for regulating cell expansion and apoptosis in different natural procedures, including tumor advancement. Moreover, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), the primary controllers of adiponectin, have been ensnared in carcinogenesis in a few growths, including RCC (Ito et al., 2017). A population based as well as statistical study was done in Denmark among 335682 people to show the relationship between the use of antihypertensive drugs and cancer. This study proves about the association between antihypertensive drugs and cancer risk. For this study, they used several classes of antihypertensive drugs. They found that the result is positive In case of diuretics, ACE inhibitors, beta blockers, calcium antagonists among the people who were 30 to 85 years old (Fryzek et al., 2005). Antihypertensive drugs

supposed to decrease this amount of production but some antihypertensive drugs increase this production for example lisinopril (Yilmaz et al., 2007).

1.3.4 Prostate cancer

Prostate malignancy (PC) is the most regular disease analyzed in men of Western nations and the second driving reason for growth passing. In Canada half of PCs happen after the age of 70, at a minute where men are generally presented to cardiovascular medications. Cardiovascular medications, especially those utilized for the treatment of hypertension, have for quite some time been suspected to bring about disease. Aside from the association amongst diuretics and renal cell carcinoma, late surveys regarding the matter disprove this theory and even recommend that a few classes of antihypertensives could lessen growth chance. Despite the fact that the populace at most serious danger of prostate cancer is every now and again presented to these solutions, few reviews have examined the connection between prostate cancer risk and antihypertensive medication utilize. Evaluate ing this connection is applicable concerning the identification of prostate cancer hazard calculates, a superior comprehension of prostate cancer physiopathology and the inevitable advancement of new chemo preventive operator (Linda Perron, 2004). Antihypertensive medication is widely used in the developed countries. Thus, any effects these drugs might have on prostate cancer risk are likely to have public health relevance.

1.3.5 Colorectal cancer

Among all leading cancer, colorectal cancer is generally occurred in case of elder people and the mortality rate is high in developing countries. In Japan, colorectal cancer is in number one position according to mortality rate among female. This is due to the disruption of estrogen which plays an essential role in apoptosis. Disruption of estrogen inhibits the rate of apoptosis which may lead to cancer in female. But in case of colorectal cancer the rate of cancer occurrence is high for male than female due to the function of estrogen (Honma et al., 2011). Nowadays, colorectal cancer is found to be reported as an ADR of antihypertensive drugs.

1.3.6 Gastric Cancer

Gastric malignancy is assessed to represent around 10% of intrusive diseases worldwide and is the second driving reason for tumor passing. In spite of the fact that the frequency of gastric growth has been diminishing, it remains a typical threat around the world, particularly in Asia. Patients with gastric growth often encounter repetitive tumors, even after a corrective surgical resection, in light of the fact that gastric disease is as often as possible analyzed at a propelled organize. Surgical treatment alone is not helpful for patients with neighborhood and distal repeats (Liao et al., 2010). The risk of gastric cancer is three fold higher in male comparing with female in Japan and is gradually occurs the people of more than 40 years old. This may be due to the difference between hormonal factors because female hormone protects themselves against carcinogenic factors.

1.4 Susceptibility to cancer due to using antihypertensive drugs between male and female:

The ADR in case of antihypertensive drugs are higher for female than male. Again, the female whose age is less than 50 years are more prone to have ADR among all female for using antihypertensive drugs (Kajiwara et al., 2014). Previously several study report that the risk for women is 3 to 4 fold high comparing with men (Heck et al., 2010). According to the surveillance of US people, with difference of year the possibility of renal cell carcinoma is 19% higher in black people comparing with white people and in case of only black women the rate is 4% higher than white women. Data from NHANES within 1999 to 2004 said about the age related prevalence's of 39% and 28% for highly contrasting men, separately, and 41% and 27% for highly contrasting women (Waxman et al., 2008). Another study was done in Michigan and Chicago to occurrence of kidney cancer among newly diagnosed kidney patient includes both men and women with the age of 20 to 79. This study proved that among both black as well as white women hypertension is related with increased risk of renal cell carcinoma (Richardson & Hamra, 2010). Among all country worldwide, in central Europe and also in Eastern Europe the rate of occurrence of renal cancer is increased and observed in the Czech Republic. Report showed that among both 100000 men and women 20.1% are women and 10.2 % are men.

The purpose of this study is to assess the association between cancer and previous use of antihypertensive medication, taking into account the class of antihypertensive drug and the occurrence of cancer between male and female.

CHAPTER TWO

METHODOLOGY

Chapter 2: Methodology

2.1 Sources of Signal

I took data of the signal from WHO Global Pharmacovigilance Data base to identify the relationship between antihypertensive drugs and cancer. The name of database is VigiBase and this database is available for general people by a web application VigiAccess. At first signals of the specific adverse effect are collected from different sources like from healthcare professionals and non-healthcare professionals. The potential ADRs can also be arise from the report of several literatures, from irregular trials, from several studies and also from SDRs.

2.2 Signal detection

Signal detection can be done by two ways-qualitative and quantitative. Here we use quantitative method. This is a statistical method to identify drug-event pairs that occur with disproportionately high frequency in large spontaneous report databases. This method is also known as data mining. Typical methodologies used include RR, ROR, PRR, IC and EBGM. Data mining is a term that has been used to describe any computational method used to automatically and continuously extract useful information from large amounts of data. Pharmaco-surveillance methods used by regulatory agencies, information used to generate signals and the threshold for adverse drug reaction signals.

Table-1.1: Signal detection methods (I et al., 2014)

Method	**Regulatory agency**	**Information used**	**Criteria for the detection of signal**
PRR	TGA, MHRA	[A/(A + B))/(C/ (C + D)]	PRR ≥2, A ≥ 3, $X^2 \geq 4$
ROR	Netherlands Pharmacovigilance Foundation Lareb	(A/B)/(C/D)	Lower limit of 95 % CI ≥1, A ≥ 2
BCPNN	Uppsala Monitoring [(WHO) Vigibase]	Log2 [p(x,y)/ p(x)p(y)]	Lower limit of 95 % CI >0

2.3 Signaling Method

The proportional reporting ratio (PRR) was used to detect the signals for antihypertensive drugs induced adverse effect that is cancer. These methods utilize the 2 × 2 table for the signal detection. The calculation of this method is supported by the information collected by vigibase. In the European countries, United Kingdom, Australia used these signaling criteria for the detection of signal. The general criteria of PRR are- The value 'a' indicates the number of individual cases with the suspect medicinal product P involving an adverse event R. The value 'b' indicates the number of individual cases related to the suspect medicinal product P, involving any other adverse events but R. The value 'c' indicates the number of individual cases involving event R in relation to any other medicinal products but P. The value 'd' indicates the number of individual cases involving any other adverse events but R and any other medicinal products but P.

Table-2.1: 2 × 2 table of the disproportionality analysis of the proportional reporting ratio (Lerch et al., 2015)

Medicines	**Drug of interest**	**All other drugs**
Reaction of interest	a	b
All other interaction	c	d

2.4 Selection of method

One commonly used example of a measure of disproportionality is the PRR. In our study, we use this method. The calculation of the PRR is given below.

Table-2.2: Method of proportional reporting ratio

Method	**Regulatory agency**	**Information used**	**Criteria for the detection of signal**
PRR	TGA, MHRA	[a/(a + b))/(c/ (c + d)]	PRR ≥ 2, a ≥ 3, $\chi^2 \geq 4$

For the detection of signal automatically the reports which are coming from worldwide dispatched and then it aggregated as a form of contingency table. We have used a

statistical tool which is VigiAccess to generate the signal of proportionate approach which uses the stability of a considerably large size of database. This includes estimation of the proportion of certain reaction for cancer in which the comparator is the drugs of the same group of antihypertensive drugs in the database. The after effect of such estimation is known as proportional reporting ratio (PRR) where a/a+b divided by c/c+d in a 2 × 2 contingency table is called PRR. We used the proportional reporting ratio (PRR) to find out the specific adverse event for a specific drug. Here the adverse event is cancer for antihypertensive drugs (Pizzoglio et al., 2012)**.** The strength of the signal can be calculated by determining the value of PRR and chi-square. Chi-square value is mainly used in VigiAccess in the system of data analysis. The Chi-square is used as an alternative measure of association between the medicinal product P and the adverse event R based on the following calculation:

$$\chi^2 = (ad - bc)^2 (a + b + c + d) / [(a + b)(c + d)(a + c)(b + d)]$$

By using the data of VigiAccess, we judged the criteria for all groups of antihypertensive drugs which showed the adverse event of cancer during the period of 2000 to 2016.

Table-2.3: Example of a PRR calculation-Lisinopril and cancer

Adverse event	**Lisinopril**	**All other drugs**	**Total**
Cancer	378	215	a+b= 593
All other interaction	40822	76642	c+d=117464
Total	a+c= 41200	b+d=76857	a+b+c+d=118057

PRR= 378/41200 divided by 215/76857 = 3.21

Chi-square value= 218.26

Like this calculation we found the result of PRR and chi-square for all antihypertensive drugs we choose for our study.

CHAPTER THREE

RESULT

Chapter 3: Result

Table: 3.1: Pharmacovigilance study of antihypertensive drugs

Group of Antihyper-tensive drugs	Drug substance	Number of reports(a)	No. of reports: Female	No. of reports: male	PRR value	Chi-square value
ACE inhibitors	Lisinopril	378	62%	38%	3.21	218.26
	Captopril	58	75%	25%	0.039	51.45
	Enalapril	52	41%	59%	0.18	175.67
	Quinapril	90	69%	31%	3.78	157.02
	Ramipril	113	51%	49%	0.97	0.04
Beta blocker	Metoprolol	609	56%	44%	2.77	219.34
	Atenolol	191	63%	37%	0.61	39.04
	Betaxolol	7	100%	0%	0.34	8.68
	Bisoprolol	61	37%	63%	0.47	34.48
	Propranolol	81	67%	33%	0.41	59.48
Calcium Channel Blockers	Amlodipine	508	56%	44%	2.16	72.717
	Verapamil	84	45%	55%	0.62	16.23
	Felodipine	28	58%	42%	0.38	27.31
	Nifedipine	167	47%	53%	0.65	23.57
Diuretics	Furosemide	150	52%	48%	0.62	6.593
	Bumetanide	8	10%	90%	1.06	0.03
	Metolazone	4	63%	37%	0.566	1.292
	Torasemide	22	35%	65%	1.63	4.69
	Thiazide	157	49%	51%	2.09	9.87
Angiotensin II receptor blockers	Losartan	119	60%	40%	0.42	76.619
	valsartan	447	54%	44%	2.90	189.32
	Eprosartan	33	67%	33%	1.82	11.898
	Irbesartan	73	51%	49%	0.45	43.95

3.1 Relationship between antihypertensive drugs and cancer

The relationship can be explained from table 3.1 that there is relationship between antihypertensive drugs and cancer.

3.1.1 ACE inhibitors

Among all ACE inhibitors, some give high report for cancer as an ADR. These are lisinopril, captopril, enalapril, quinapril and ramipril. From table 3.1, it is clear that the number of reports for lisinopril is 378 and this number is higher than other drugs of ACE inhibitors. Again, for captopril, enalapril, quinapril and ramipril this number is 58, 52, 90 and 113. Although the number of reports is only high just for lisinopril but this is not the only drug of ACE inhibitors which show the positive PRR value. PRR value is the value which is used to find out the positive and negative result for an adverse drug reaction of a drug. From table 3, we know that the result of PRR will be true if the value of PRR is more than 2. The PRR value for lisinopril, has high amount of report, is 3.21. Further the PRR value for captopril, enalapril, quinapril and ramipril is respectively 0.039, 0.18, 3.78 and 0.97. From this value, it is easy to perceive that the PRR value is also positive for quinapril that is 3.78. This means quinapril has the potential to show cancer as an ADR. But the PRR value cannot prove the positive result of the ADR alone. The result is also dependent on chi-square value. When PRR and chi-square these both will show the positive value only then we will get the actual positive value. So here the chi-square value for lisinopril, captopril, enalapril, quinapril and ramipril is respectively 218.26, 51.45, 175.67, 157.02 and 0.04. Chi-square value is positive for lisinopril, captopril, enalapril and quinapril. In case of ramipril the result is negative because it is clear from table-2.2 that if the number of report is more than 3 and chi-square value is more or equal to 4 only then the result is positive. So, by analyzing both the PRR and chi-square value we can say that lisinopril and quinapril show the positive result among all ACE inhibitors because the value of PRR is more than 2 and chi-square value is more than 4.

3.1.2 Beta blockers:

The beta blocker drugs which mainly show cancer as a higher adverse drug reaction are metoprolol, atenolol, betaxolol, bisoprolol and propranolol. It is clear if we see table-3.1 that among all drugs of beta blocker group the number of signal is higher for metoprolol and the total number of report is 609. On the other hand, the number of signal for

atenolol, betaxolol, bisoprolol and propranolol is 191, 7, 61 and 81 but this number is much lower from metoprolol. From table 3.1, we know that the result of PRR will be true if the value of PRR is more than 2. Further from the same table we come to know that if the report is more than 3 and chi-square value is more or equal to 4 only then we can say that the result is positive. So, after determining the PRR value and chi-square value, the value of PRR is more than 2 and chi-square value is 219.34 for only one beta blocker and that is metoprolol. For other drugs like atenolol, bisoprolol, betaxolol and propranolol the PRR value is less than 1. But chi-square values of all beta blockers show positive result which prove that somehow there is some relationship between beta blockers and cancer.

3.1.3 Calcium Channel Blockers

The calcium channel blockers which mainly show cancer as a higher adverse drug reaction are amlodipine, verapamil, felodipine and nifedipine. From table 3.1, it is clear that the number of reports for amlodipine is higher than other drugs of CCBs and nifedipine is fall under 2^{nd} position. Therefore, the number of reports for amlodipine and nifedipine are 508 and 167. The other drugs of CCBs are verapamil and felodipine and the number of reports for them are respectively 84 and 28 which are much lower than the others. From table 3.1, we know that the result of PRR will be true if the value of PRR is more than 2. The PRR value for amlodipine, verapamil, felodipine and nifedipine are respectively 2.16, 0.62, 0.38 and 0.65. Therefore the PRR value is positive only for amlodipine which is 2.16 but for others this value is negative because the value is less than 1. The positive or negative result is not only dependent on PRR value but also dependent on the number of reports and chi-square value. From the table-3, it is easy to understand that if the report is more than 3 and chi-square value is more or equal to 4 only then the result is positive. So, the chi-square value for amlodipine, verapamil, felodipine and nifedipine is respectively 72.717, 16.23, 27.31 and 23.57. The chi-square value is positive for all the drugs. After combining the number of reports, PRR value and chi-square value the result is only positive for amlodipine because only for amlodipine the number of reports, PRR value and chi-square value is respectively 508, 2.16 and 72.717.

3.1.4 Diuretics

The diuretics which mainly show cancer as a higher adverse drug reaction are furosemide, bumetanide, metolazone and torasemide. The number of reports is different for each drug. From table 3.1, it is clear that the number of reports for furosemide, bumetanide, metolazone and torasemide is respectively 150, 8, 4 and 22. Therefore, the number of reports is higher for furosemide than others. From table 3.1, we know that the result of PRR will be true if the value of PRR is more than 2. The PRR value of furosemide, bumetanide, metolazone and torasemide are 0.62, 1.06, 0.566 and 1.63. From the table-2.2, it is easy to understand that if the report is more than 3 and chi-square value is more or equal to 4 only then the result is positive. The chi-square value for furosemide, bumetanide, metolazone and torasemide is respectively 0.62, 1.06, 0.566 and 1.63. After combining the number of reports, PRR value and chi-square value the result is negative for all diuretics.

3.1.5 Angiotensin II receptor blockers

Among all Angiotensin II receptor blockers, some give high report for cancer as an ADR. These are losartan, valsartan, eprosartan and irbesartan. From table 3.2, it is clear that the number of reports for valsartan is 447 and this number is higher than other drugs Angiotensin II receptor blockers. Again, for losartan, eprosartan and irbesartan this number is respectively 119, 33 and 73. PRR value is the value which is used to find out the positive and negative result for an adverse drug reaction of a drug. From table 3.2, we know that the result of PRR will be true if the value of PRR is more than 2. The PRR value for valsartan has high amount of report which is 2.90. Again for losartan, eprosartan and irbesartan the PRR value is 0.42, 1.82 and 0.45. From this value, it is easy to perceive that the PRR value is also positive for valsartan that is 2.90. This means valsartan has the potential to show cancer as an ADR. But the PRR value cannot prove the positive result of the ADR alone. . The result is also dependent on chi-square value. When PRR and chi-square these both will show the positive value only then we will get the actual positive value. So the chi-square value for losartan, valsartan, eprosartan and irbesartan are 76.619, 189.32, 11.898 and 43.95. The chi-square value is positive for all the drugs. After combining the number of reports, PRR value and chi-square value the result is only positive for valsartan.

Table 3.2: Antihypertensive drugs for high amount of signals

Antihypertensive drugs	Overall signals
Metoprolol	609
Lisinopril	378
Valsartan	447
Amlodipine	508

So overall from table 3.1 and table 3.2, we can say that there is relationship between cancer and antihypertensive drugs.

3.2 Types of antihypertensive drugs that can cause cancer

This method indicated that overall 4 drugs among the drugs listed in the table met the minimal criteria of PRR and chi-square value. The other drugs met the criteria of chi-square but not the PRR. The signals collected from VigiAccess and the calculated value of PRR and chi-square are given in table 3. Observing at different classes of antihypertensive medications, ACE inhibitors, beta blockers, calcium channel blockers and angiotensin II receptor blockers are associated with cancer.

3.2.1 ACE inhibitors

The chi-square value is positive for all drugs except ramipril. So, ramipril has no risk of exhibiting cancer as an adverse drug reaction due to its negative chi-square value and also negative PRR value. For ramipril, the PRR value is 0.04 and chi-square value is 0.97. Again, captopril and enalapril show negative PRR value and positive chi-square value. The PRR value for captopril and enalapril is respectively 0.039 and 0.18 which prove that these 2 drugs are not related with cancer. Further, for quinapril the report is low but chi-square value and PRR value is positive. The chi-square value of quinapril is 157.02 and PRR value is 3.78 that prove its association with cancer. Finally, in case of ACE inhibitors the number of reports for lisinopril is higher. So, the risk of cancer is high for lisinopril as its PRR value is 3.21 and chi-square value is 218.26.

3.2.2 Beta blockers

Among all beta blockers the number of reports for metoprolol is high, the PRR value and chi-square value is also high, from table 3.1. Its PRR value is 2.77 and chi-square value

is 219.34. All this value proves the association between cancer and metoprolol. Again, other beta blockers are atenolol, betaxolol, bisoprolol and propranolol. For propranolol, the chi-square value is also high but the PRR value is very low. The chi-square value for propranolol is 59.48 and the PRR value is 0.41. The number of reports and chi-square value is positive in this case but the PRR value is negative for propranolol which proves that there is no relation between propranolol and cancer. For atenolol the number of report and chi-square value is high which is respectively 191 and 39.04. So, both of this value is positive for atenolol to cause cancer as an ADR. But the PRR value is 0.61 which is a negative value for atenolol. As the PRR value is less than 2, so there is no association between cancer and atenolol. For bisoprolol the chi-square value is 34.48 which is not that much less. Among all beta blockers this value is low for betaxolol and the value is 8. So for all the drugs of beta blocker the chi-square value is positive. But, PRR value is negative for all beta blockers except metoprolol which turn all the positive chi-square value negative if we want to determine the ADR. The PRR value of atenolol, betaxolol, bisoprolol and propranolol is respectively 0.61, 0.34, 0.47 and 0.41. So, the risk of cancer is comparatively high for metoprolol than other beta blockers.

3.2.3 Calcium Channel Blockers

The chi-square value, PRR value and the total number of reports are only positive for amlodipine. Among all the drugs of CCBs the high numbers of reports come for amlodipine and this number is 508 which are high among all the antihypertensive drugs shown in table 3.2. From table 3.1, the PRR value of amlodipine is 2.16 which is a positive value and the chi-square value of amlodipine is 72.717 that is also a positive value. The other drugs of CCBs are verapamil, felodipine and nifedipine. The chi-square value is low for verapamil that is 16.23 but still this is a positive value because this value is higher than 3. Again, the other 2 drugs, felodipine and nifedipine, the chi-square value are 27.31 and 23.57 which is a positive value for both of them. But the PRR value of verapamil is 0.62 which is a negative value as this value is less than 2. So, verapamil is not associated with cancer because of its negative PRR value. Further, the number of report for felodipine is 28 which is a true number and the PRR value is 0.38. But the PRR value is negative for felodipine which prove that felodipine is not associated with cancer. At last, the number of reports for nifedipine is high and this amount is 167. The

PRR value of nifedipine is 0.65 which is a negative value which proves that nifedipine has no relationship with cancer.

3.2.4 Diuretics

From table 3.1, we found that, the total numbers of reports are only high for two drugs which are furosemide and thiazide. But for other drugs like bumetanide, metolazone and torasemide this number is extremely low. Not only the number of reports but also the chi-square value and PRR value are also low comparing with other antihypertensive drugs. Though the number of report is high for furosemide but the PRR value is low for this drug. But the chi-square value is positive for furosemide. Again for thiazide the number of report is moderately high and the PRR value is more than 2 as well as chi-square value is more than 3. These all value including number of reports, PRR value and chi-square value prove that thiazide has the link with cancer. So after combining all the value from table 3.1, we get that, the overall reports for furosemide is 150, the chi-square value is 6.593 and the PRR value is 0.62 in which the PRR value is only negative and the other value is positive. But as the PRR value is negative so furosemide is not associated with cancer. Again for bumetanide the number of report is really low and the chi-square as well as the PRR value is also low. The total reports found in VigiAccess are 8, the chi-square value is 0.03 and the PRR value is 1.06. Metolazone is also a diuretic which we choose to determine its association with cancer. The number of reports for metolazone is lower than all other diuretics. The PRR value and chi-square value is also low for metolazone. The number of reports for metolazone is 4 and the PRR value is 0.566. Again, the chi-square value for metolazone is also less than 3 that is 1.292 which is also a negative value. So after analyzing all the value we see that the PRR value and chi-square value is negative for metolazone which proves that it is not related with cancer. At last, the number of reports for torasemide is also low in number. Beside this, the PRR and chi-square value is also low. The PRR value of torasemide is 1.63 which is less than 2 and the chi-square value 4.69. Here the chi-square value is only positive for torasemide as its value is more than 3 but the value of PRR is negative as it is less than 2. So torasemide is not associated with cancer. This all value proves that diuretics are not associated with cancer.

3.2.5 Angiotensin II receptor blockers

After searching the VigiAccess, the reports of new cancer for ARBs are huge in number mainly for two drugs, losartan and valsartan. The reports for valsartan are in high among all ARBs that is 447 comparing with losartan shown in table 3.1. For losartan this amount is 119 which are significantly less than valsartan. For ARBs, the chi-square value for valsartan is 189.32 which are really high and the PRR value is 189.32. The number of reports, chi-square value and PRR value prove the strong association between cancer and valsartan. For eprosartan the number of report is positive as it is 33 and the chi-square value is also positive as the value is 11.898 which are more than 3. But the PRR value is negative in this case as the value is 1.82 which is approximately close to 2. So, there is no association between eprosartan and cancer. Again, for irbesartan the numbers of reports are 73 which is a positive value and chi-square value is 43.95 which is also positive. But due to the negative PRR value (0.45), there is no relationship between ARBs and cancer. Again the chi-square value for losartan 76.619 and it is a positive value. So, the chi-square value is positive for all drugs. But the PRR value, mainly important for determining the adverse effect, is only positive for valsartan. Although the report for losartan is also not that much less but still the PRR value we determined was negative for this drug.

Table-3.3: PRR value for antihypertensive drugs

Group of Antihypertensive Drugs	**Drugs**	**PRR value**	**Chi-square value**
ACE inhibitors	Lisinopril	3.21	218.26
ACE inhibitors	Quinapril	3.78	157.02
Beta blockers	Metoprolol	2.77	219.34
Calcium Channel Blockers	Amlodipine	2.16	72.717
Diuretics	Thiazide	2.09	9.87
Angiotensin II receptor blockers	Valsartan	2.90	189.32

3.3 Types of cancer due to using antihypertensive drugs

3.3.1 ACE inhibitors

Among all ACE inhibitors, some give high report for cancer as an ADR. These are lisinopril, captopril, enalapril, quinapril and ramipril. From table 3.2, we found that the number of report is high for lisinopril from the observed drugs and the number is 378. Various types of cancer are reported for this drug. From table 3.4, we found that the common types of cancer which is reported in high amount are- breast cancer, prostate cancer, neoplasm malignant, bladder cancer, skin cancer and thyroid cancer. The effect of ACE inhibitors on the development of renal cancer, gastric cancer, pancreatic carcinoma, bone cancer, uterine cancer and ovarian cancer are also not less significant. There are also found some increased cases of new cancer just in neoplasm stage. Again, for captopril, there are also some reports for breast cancer, skin cancer, bladder cancer and renal cancer but these cases are not in high number. Further, for quinapril the number of report is high for neoplasm malignant, colon cancer, prostate cancer, thyroid cancer and breast cancer. Furthermore, the other 2 drugs which are enalapril and ramipril, the number of case is not high but the occurrence of skin cancer is reported in significant amount.

Table-3.4: Reports of cancer for ACE inhibitors

		Types of cancer							
Drugs		NM	BRC	PC	LNM	BC	SC	CC	GC
	Captopril	8	2	8	5	1	3	8	4
	Ramipril	5	13	0	4	2	11	4	3
	Lisinopril	39	67	22	25	12	13	12	5
	Quinapril	10	13	15	7	9	14	15	19
	Enalapril	5	2	0	2	1	3	0	1

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.2 Beta blockers

Metoprolol, atenolol, betaxolol, bisoprolol and propranolol are the drugs which we observed from beta blockers. From table 3.2, the numbers of reports are high for metoprolol and we get the positive PRR and chi-square value. The occurrence of breast cancer, prostate cancer, skin cancer, colon cancer and neoplasm malignant are high in number, according to table 3.5. Many reports are found which are in neoplasm stage. To illustrate, lung neoplasm, brain neoplasm, thyroid neoplasm and hepatic neoplasm. Endometrial cancer, uterine cancer, ovarian cancer, thyroid cancer, pancreatic cancer is some other types of cancer which are reported highly. Again, for atenolol the number of report is high for neoplasm malignant, breast cancer and prostate cancer. For betaxolol, the numbers of reports are very low and the reports are found only for neoplasm malignant. In addition, skin cancer, rectal cancer and breast cancer is common for bisoprolol. Some other types are colon cancer, gallbladder cancer, hepatic cancer, bile duct cancer, basal cell carcinoma etc. But these all are low in number. The number of report for propranolol is 81 and phaeochromocytoma, Neoplasm malignant are reported in high number.

Table-3.5: Reports of cancer for beta blockers

	Types of cancer								
Drugs		NM	BRC	PC	LNM	BC	SC	CC	GC
	Metoprolol	102	79	38	35	14	23	18	7
	Atenolol	14	15	11	8	7	3	3	6
	Betaxolol	3	2	0	1	0	0	0	1
	Bisoprolol	5	4	3	2	1	7	2	0
	Propranolol	11	2	1	1	1	3	1	1

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.3 Calcium Channel Blockers

Among all drugs of Calcium Channel Blockers the number of report is in significant only for amlodipine and this number are 508, from table 3.2. According to table 3.6, the occurrence of neoplasm malignant, breast cancer, prostate cancer, lung neoplasm malignant, colon cancer and pancreatic carcinoma are significant in number. There are also found some increased cases of new cancer just in neoplasm stage. To illustrate, breast neoplasm, thyroid neoplasm, hepatic neoplasm, pancreatic neoplasm and lung neoplasm are common among this types. Some other types of cancer are also found to be reported but these are not significant in number like hepatic cancer, ovarian cancer, bone cancer, uterine cancer, throat cancer etc. Again the number of cases is also higher for nifedipine also and the significant numbers of cases are for gastric cancer, prostate cancer and colon cancer. Some others are not high in number like hepatic cancer, renal cancer, thyroid cancer, skin cancer, laryngeal cancer etc. In addition, for verapamil and felodipine the numbers of cases are lower than amlodipine and nifedipine. The report of cancer for verapamil and felodipine is respectively 84 and 28. Among all cancer types, breast cancer and neoplasm malignant is common for both verapamil and felodipine. The frequency for the occurrence of ovarian cancer, gastric cancer, colon cancer, renal cancer and skin cancer is low in number.

Table-3.6: Reports of cancer for Calcium Channel Blockers

Types of cancer									
Drugs		NM	BRC	PC	LNM	BC	SC	CC	GC
	Amlodipine	59	71	41	26	9	12	4	7
	Verapamil	11	10	14	10	3	1	1	3
	Felodipine	5	2	0	2	0	2	2	2
	Nifedipine	30	23	13	14	6	10	10	14

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.4 Diuretics

Among all diuretics the commonly used drugs for hypertension are furosemide, bumetanide, metolazone and torasemide. From table 3.7, for furosemide, the occurrence of neoplasm malignant (13), breast cancer (6), prostate cancer (10), lung neoplasm malignant (7), colon cancer (4), skin cancer(11), bladder cancer (2) and gastric cancer (8) are significant in number. Some other types of cancer which are found in low number are marrow hyperplasia (3), non-small cell lung cancer (3), prostate cancer metastatic (3), throat cancer (3), uterine leiomyoma (3), basal cell carcinoma (2), Bone cancer (2), Bowen's disease (2), gammopathy (2), haemangioma (2), haematological malignancy (2), hepatocellular carcinoma (2), leukaemia (2), lymphoma (2), malignant melanoma (2), malignant neoplasm progression (2), metastases to lung (2), metastasis (2) etc. There are also found some increased cases of new cancer just in neoplasm stage. To illustrate, breast neoplasm, thyroid neoplasm, hepatic neoplasm, pancreatic neoplasm and lung neoplasm are common among this types. The number of report for bumetanide is very low and the types of cancer are breast cancer (2), skin cancer (2) as well as lung neoplasm malignant (1). Again for metolazone, the number is very low and report come only for prostate cancer and lung neoplasm malignant. Further for torasemide the reports are mainly come for 2 types of cancer that are neoplasm malignant (5) and lung neoplasm malignant (4). Some other types of cancer which are also reported in low number are prostate cancer (1), skin cancer (1), colon cancer (2) and gastric cancer (1).

Table-3.7: Reports of cancer for Diuretics

	Types of cancer							
Drugs		NM	BRC	PC	LN	SC	CC	GC
	Furosemide	13	6	10	7	11	4	8
	Bumetanide	0	2	0	2	1	0	0
	Metolazone	0	0	1	1	0	0	0
	Torasemide	5	0	1	4	1	2	1
	Thiazide	17	16	5	5	4	2	5

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.5 Angiotensin II receptor blockers

Among all drugs of angiotensin II receptor blockers the number of report is in significant only for valsartan and this number are 447. We found from VigiAccess which are shown in table 3.8, the occurrence of neoplasm malignant (61), breast cancer (58), Renal cancer (16), prostate cancer (28), pancreatic carcinoma (9), thyroid cancer (9), lung neoplasm malignant (25), bladder cancer (10), skin cancer (5), colon cancer (21) and gastric cancer (6) are high in number. Some other types of cancer are also found to be reported but these are not significant in number like hepatic cancer, ovarian cancer, bone cancer, uterine cancer, throat cancer etc. There are also found some increased cases of new cancer just in neoplasm stage. To illustrate, Brain neoplasm (12), breast neoplasm, gastrointestinal neoplasm (4), hepatic cancer metastatic (4), metastatic neoplasm (4), thyroid neoplasm (4), neoplasm (9), hepatic neoplasm, pancreatic neoplasm and lung neoplasm are common among this types. Again, for losartan, the total number of cases are 119 and the occurrence of neoplasm malignant (16), breast cancer (9), Renal cancer (5), prostate cancer (6), pancreatic carcinoma (9), thyroid cancer (9), lung neoplasm malignant (12), bladder cancer (4), skin cancer (12), colon cancer (4) and gastric cancer (5) are high in number which are shown in table 3.8. The reports are also come for some other cancers which are not high in number like esophageal carcinoma (4), pancreatic carcinoma (4), basal cell carcinoma (3), colon cancer (3), neoplasm (3), non-Hodgkin's lymphoma (3), plasma cell myeloma (3), renal cell carcinoma (3), squamous cell carcinoma (3), uterine leiomyoma (3), bile duct cancer (2) etc. The cancers which are found in neoplasm stage are biliary neoplasm (1), bladder neoplasm (1), hepatic neoplasm (1), colon neoplasm (1), salivary gland neoplasm (1) etc. Further, for eprosartan the occurrence of neoplasm malignant (7), breast cancer (2), Renal cancer (1), prostate cancer (2), lung neoplasm malignant (2), bladder cancer (1), skin cancer (4), colon cancer (2) and renal cancer (1) are mainly found which are given in table 3.8. At last, the reports for irbesartan, which is an antihypertensive drug of ARBs group, are high only for neoplasm malignant (13), breast cancer (8), skin cancer (9) and renal cancer (5).

Table-3.8: Reports of cancer for Angiotensin II receptor blockers

Types of cancer									
Drugs		NM	BRC	PC	LNM	BC	SC	CC	RC
	Losartan	16	9	6	12	4	12	4	5
	Valsartan	61	58	28	25	10	5	21	16
	Eprosartan	7	2	2	2	1	4	2	1
	Irbesartan	13	8	2	3	1	9	1	5

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.4 Susceptibility to cancer due to using antihypertensive drugs between male and female

3.4.1 ACE inhibitors

From all ACE inhibitors shown in table 3.1, the number of reports for female is high compare to male except enalapril. In case of enalapril, the percentage of reports for female is 41% where this percentage is 59% for male. Otherwise the other drugs of ACE inhibitors like lisinopril(female-62%), captopril(female-75%), quinapril(female-69%), ramipril(female-51%) female is more susceptible to cancer than male.

3.4.2 Beta blockers

Again from all beta blockers shown in table 3.1, the number of reports for female is high compare to male except bisoprolol. In case of bisoprolol, the percentage of reports for female is 37% which is very low in percentage than male. Otherwise the other drugs of beta blockers like metoprolol (female-56%), atenolol (female-63%), betaxolol (female-100%), Propranolol (female-67%) female is more susceptible to cancer than male.

3.4. 3. Calcium Channel Blockers

Further from all calcium channel blockers shown in table 3.1, the number of reports for female is high compare to male except verapamil (female-45%) and nifedipine (female-

47%). Otherwise the other drugs of beta blockers like amlodipine (female-56%) and felodipine (female-58%) female is more susceptible to cancer than male.

3.4. 4 Diuretics

Furthermore, from all diuretics shown in table 3.1, the number of reports for female is high compare to male except bumetanide (female-10%) and torasemide (female-35%). Otherwise the other drugs of diuretics like furosemide (female-52%) and metolazone (female-63%) female is more susceptible to cancer than male.

3.4. 5 Angiotensin II receptor blockers

At last from all angiotensin II receptor blockers shown in table 3.1, the number of reports for female is high compare to male for all drugs like losartan (female-60%, male-40%), valsartan (female-54%, male-44%), eprosartan (female-67%, male-33%) and irbesartan (female-51%, male-49%) and metolazone (female-63%) female is more susceptible to cancer than male.

CHAPTER FOUR

DISCUSSION

Chapter 4: Discussion

In this pharmacovigilance study, we found that all the antihypertensive drugs are not associated with cancer and only some specific drugs are mainly show cancer as adverse drug reactions. This study completely incorporated all the data that are available on VigiAccess. VigiAccess is a database published the data of ADRs which are compiled by WHO. These all data are also posted in different way in several databases collected by several organizations, an extremely useful source for pharmacovigilance study. The Proportional Reporting Ratio, an established method, is mainly used for the determination of ADRs for specific drug. Nevertheless we also used chi-square value to strengthen our findings. The risk for the occurrence of new cancer is also significant. Regardless the reason of the increased risk of cancer due to antihypertensive drugs is still unknown.

4.1 Relationship between antihypertensive drugs and cancer

The results from the pharmacovigilance study about the association between antihypertensive drugs and cancer show that all the antihypertensive drugs do not show cancer as their ADR. Only some specific drugs exhibit cancer and these are mainly those drugs which are highly used. The most of the researches were according to hospital based as well as examined different cancer sites. Most studies were small in size and had relatively short follow-up period. But we took all the data from a large database and this is long follow-up period.

4.1.1 ACE inhibitors

Primarily ACE inhibitors are used to reduce the elevated blood pressure as well as in the congestive heart failure. Among all the ACE inhibitors lisinopril is used widely worldwide. The outcome of Pharmacovigilance study by using the method quantitative signal detection for ACE inhibitors show that all the drugs of this group are not associated with cancer. In our study, we found that only lisinopril and quinapril among all the ACE inhibitors show that it is associated with cancer but other drugs do not due to their negative PRR and chi-square value. It can be because lisinopril is the one of thehighly used antihypertensive drugs around the world, according to drugs.com and in

2016; lisinopril was in number 3 positions. Among all the antihypertensive drugs prescribed among the whole world lisinopril was in first place. Again, in 2011 and 2014, lisinopril was the antihypertensive drug which is prescribed in high amount. There were about 104 million lisinopril prescriptions filled in 2014, according to web med and in 2011 this amount is around 87.4 million. As this is a highly used drug, so it is predictable that the reports will also high for this drug. Again, quinapril is another ACE inhibitor which used in heart failure and also for some other purposes. For quinapril the numbers of reports are not that much high but still it quinapril show its link with the risk of cancer. But when we saw different study about the relationship among ACE inhibitors and cancer, we found some neutral effect. Some study said about their relationship but some are not. Finally, from our study we prove that all the ACE inhibitors are not related with cancer risk and only those drugs are related with cancer which has high amount of reports in VigiAccess.

4.1.2 Beta-blockers

In the treatment of hypertension beta blocker are used increasingly and their action is almost like diuretics on heart disease and stroke. In the management of heart failure and reduce the mortality rate beta blocker is useful. In case of young patient, the first line drug for hypertension is beta blocker (Ong, 2007). In recent years this drug has found to be a risk of cancer in increased amount. In past years, the data about the occurrence of cancer is insufficient. But at present years, databases protect all the data of ADRs. In case of β-Blockers the data for metoprolol is sufficient about the occurrence of cancer. For this reason, it was easy for our study to find out our drug of interest to determine the result for the occurrence of the risk of cancer in case of metoprolol. In our study, the number of report is high enough to guess that metoprolol is related with the risk of cancer. But still we go for pharmacovigilance study to meet our estimation. At the same time, when we go for some other drugs like atenolol, betaxolol, bisoprolol and propranolol to find out the number of reports of cancer for this drugs. We found there is no link between these drugs and cancer which prove that all drugs of beta blockers are not associated with the risk of cancer.

4.1.3 Calcium Channel Blockers

For the treatment of hypertension CCBs are widely prescribed as an antihypertensive drug and also in the treatment of coronary heart disease. Calcium channel blocker is one

of the common types of antihypertensive drugs which used since two decades to treat the hypertension. Some researchers raise a question by doubting that these drugs are responsible for heart attack. Recently some study said about the association between these agents and malignancy. In our study, we show that, all the CCBs are not associated with cancer. Our other drugs of interest for CCBs are verapamil, felodipine and nifedipine. Only for amlodipine, the chi-square as well as PRR value is positive which prove that the signal for amlodipine is true. Amlodipine is a first line agent for the treatment of hypertension and used for around two decades. But for other drugs like verapamil, felodipine and nifedipine the PRR value is negative which prove that these three drugs do not have any risk for cancer.

4.1.4 Diuretics

Diuretics are the most common type of drug prescribed in case of hypertension. The result of our study reveals that diuretics are not associated with the risk of cancer. We mainly work with furosemide, bumetanide, metolazone and torasemide. But many studies are done to prove about the relationship between the use of diuretics and risk of cancer. One of the primary reviews proposing that diuretic treatment may be related with carcinoma originated from some interviewed based study. This interview revealed that cancer is a risk factor for diuretic only in women. Again, after these studies researchers wanted to know more about the relationship between diuretics and antihypertensive drugs. They all got positive result about the association between them and the affected people are generally the long term user of antihypertensive drugs. Utilization of both thiazide and potassium-sparing diuretics was related with modest chance of breast carcinoma. Further, long term utilization of these sorts of diuretics was related with high risk of breast carcinoma. A diuretic especially thiazide diuretics is used for the primary treatment of hypertension and it has the ability to increase the risk of renal carcinomas (Keith T. Flaherty1, 2005).

4.1.5 Angiotensin II receptor blockers

Angiotensin II receptor blockers are the primarily given successful drugs for hypertension patients and patients who are intolerance with other inhibitors will get benefit by this drugs in several heart disease for example stable coronary heart disease. The tolerability is proven good and effective in case of Angiotensin II receptor blockers

and around 25% of patients suffering from hypertension are taking this drug worldwide. Angiotensin-receptor blockers (ARBs) are used widely as an antihypertensive drug and at first approved in 1995 for clinical purpose. Losartan is the first discovered drug as ARBs. According to safety data which were found after several trials always gave a positive image about the tolerability of ARBs but some recent decade experiments shown that RAAS (the renin–angiotensin–aldosterone system) has some effects which can make serious harm on human body like cancer. Angiotensin II receptor blocker has the ability to increase the risk of cancer (Olin et al., 2011). The outcome of our study show that only valsartan is related with cancer risk among all the drugs we studied from ARBs. We studied with the drugs losartan, valsartan, eprosartan, irbesartan and they showed no association with cancer. The reports for valsartan were high enough to predict its association with cancer. The report for losartan is moderately high but the report for eprosartan as well as irbesartan is very low comparing to valsartan.

4.2 Types of antihypertensive drugs that can cause cancer

As an initial therapy different types of antihypertensive drugs are used to control the blood pressure effectively. By regulating the electrolyte balance as well as blood pressure hypertension can be treated. For the significant reduction of hypertension and its associated morbidity as well as mortality these drugs are effectively worked. To control the blood pressure effectively patients require combination of drugs, maximum time at least two or more drugs which may lead to several adverse effect. The most common type of antihypertensive drugs are vasodilator, ACE inhibitor, diuretics, adrenergic blockers, angiotensin II receptor blockers, calcium channel blockers, beta blockers and alpha blockers. Thiazide diuretic is used as the treatment of first line for people who has high BP. (Arroll et al., 2008) Many study said that diuretics and calcium channel blocker is mainly responsible for cancer (A. M. Lindgren et al., 2005). But according to our study, some specific drugs from all the groups of antihypertensive drugs are associated with cancer. To sum up, all the drugs of antihypertensive drugs are not related with the risk of cancer.

4.2.1 ACE inhibitors

In the treatment of heart failure, management of renal insufficiency is really important to reduce the mortality rate and ACE inhibitors are most commonly used therapeutic agent in this case. To reduce the mortality rate due to heart failure ACE inhibitors is a standard

medication which is proved by major studies. But again the possibility of adverse drug reactions is high in case of ACE inhibitors among the patients. When we saw different study about the relationship among ACE inhibitors and cancer, we found some neutral effect. Some study said about their relationship with cancer but some are not. So, we go for a pharmacovigilance study to sort out this problem. In the result of our study we found that all ACE inhibitors are not associated with cancer. We choose five drugs as our drug of interest to find out the link and among them two drug show their association with cancer and other three drugs do not show their association. We studied with lisinopril, captopril, enalapril, quinapril and ramipril. Among these drugs lisinopril and quinapril has the risk for cancer as the signal for both of the drugs are true because of its moderately high PRR value. For captopril, enalapril and ramipril the PRR value is low which prove that these drugs are not associated with cancer.

4.2.2 Beta-blockers

To meet our expectation we go for the pharmacovigilance study and use the PRR method which is fall under quantitative method in pharmacovigilance. So, after using this method we found that metoprolol is moderately linked with the risk of cancer. The report for metoprolol is high enough to estimate that metoprolol is linked with the risk of cancer. Then to prove our theory we used our data and go for a pharmacovigilance study by using quantitative method (PRR and chi-square method). Like metoprolol, we use the data of all reports from VigiAccess for atenolol, betaxolol, bisoprolol and propranolol and use the same quantitative method which proves that these drugs are not linked with the risk of cancer. If beta blocker is used for more than 10 years there is a possibility of increased risk of cancer. Due to using atenolol for a long period of time the risk is increased. Beta blocker, bisoprolol also related with higher risk of cancer (Leung, Hung, Chan, & Mou, 2015).

4.2.3 Calcium Channel Blockers

After observing the results of CCBs, amlodipine is the only drug which has the risk to cause cancer. By altering the intracellular extent of calcium, it makes a change in the action of programmed cell death. As a result, destruction of the damaged cell cannot be done properly and this may develop cancer. Calcium keeps an important role in the process of apoptosis. So, this can be a reason for the occurrence of cancer for calcium

channel blockers. Again, by the process of mitochondrial permeabilization as well as by stimulating phagocytosis calcium is involved in the cell death. So, through this way calcium helps to prevent cancer. But calcium channel blockers mainly block the action of calcium and increase the risk of cancer. A study was conducted for the analysis of association for duration of using antihypertensive drugs and cancer risk by Li et al. which reported that short term use of immediate release drug specially calcium channel blocker is responsible for the cancer risk. In case of long term use, CCBs are related with cancer risk (Giordano, 2003). This can be the reason for amlodipine to be a risk factor for cancer.

4.2.4 Diuretics

From the result of our study, we found that thiazide is the only drug among all diuretics which has the moderate risk for the occurrence of cancer. Many studies are done to prove about the relationship between the use of diuretics and risk of cancer. A diuretic which is a class antihypertensive agent show that this agent has the ability for the occurrence of cancer and this drug can inhibit the cell apoptosis process after effect influence the synthesis and metabolism of insulin. A diuretic especially thiazide diuretics is used for the primary treatment of cancer and it has the ability to increase the risk of renal carcinomas. (Keith T. Flaherty1, 2005) But the excess risk was found for those who were using antihypertensive drugs for more than 5 years (Wong-Ho Chow, 1995). So, this study proved that long term use of diuretics is responsible for the occurrence of cancer. A study was done in Seattle–Puget Sound metropolitan area among women of 65–79 years and reported that both short and long durations of use of these types of diuretics were associated with increased risks of carcinoma (C. I. Li et al., 2003).

4.2.5 Angiotensin II receptor blockers

Angiotensin II receptor blockers are the primarily given successful drugs for hypertension patients and patients who are intolerance with this inhibitors will get benefit in several heart disease for example stable coronary heart disease. The tolerability is proven good and effective in case of Angiotensin II receptor blockers and around 25% of patients suffering from hypertension are taking this drug worldwide. But A clinical study in 2014 and CHARM-Overall study, LIFE study, ONTARGET and TRANSCEND studies, VALIANT studies prove the association of cancer due to using Angiotensin II

receptor blockers (Dezsi, 2014). But according to research database of UK they did not get any evidence about their association in a large amount but they detect small risk about the breast and prostate cancer among the patients (Bhaskaran, Douglas, Evans, van Staa, & Smeeth, 2012). According to the result of our study, all angiotensin II receptor blockers are not associated with the risk of cancer. Only valsartan is moderately proved to be a risk for cancer as stated by our study. Other drugs which we considered for our pharmacovigilance study are not linked with cancer as the number of reports as well as the PRR value is low.

4.3 Types of cancer due to using antihypertensive drugs

Different types of cancer like Prostate cancer, breast cancer, colon cancer, throat cancer, renal cancer, skin cancer can occur due to using antihypertensive drugs though the number is low but there is possibility to occur (Calle, 2007). Some cases show about the association between antihypertensive drugs and cancer but while some are not. Due to change the formulation of drugs like sustained release or immediate release the risk of this type of occurrence increase. Some study said about the inhibition of apoptosis due to using antihypertensive agents thus some show that this can facilitate cell division with the potential of malignant which increase the risk associated with breast cancer. Several preclinical studies reported that it has the ability to cause cancer and it possesses the property of chemo preventive in case of cancer. (1-pancreatic) A study was done by using the data of the Longitudinal Health Insurance Database 2000 (LHID2000), which show the positive result between the uses of antihypertensive drugs with thyroid cancer. (thyroid-1) Among all dangerous as well as fatal diseases cancer is one and nowadays the most common cancer among all women is breast cancer. Due to breast cancer the mortality rate among women is increasing and antihypertensive drugs has the ability to cause cancer (Yu & Wang, 2016). Adipose tissue is responsible for the synthesis and secretion of adiponectin. Increase production of adiponectin may involve in the occurrence of breast cancer because some antihypertensive drugs increase the production of adiponectin (Liu et al., 2016). Worldwide the number of cases for skin cancer is increasing due to the exposure of ultraviolet radiation on the skin. The occurrence of skin cancer due to using antihypertensive drugs totally depends on duration and intensity of drug use. Among all types of skin cancer basal cell carcinoma is most common. Other common types of skin cancer are squamous cell skin carcinoma and malignant

melanoma. In case of basal cell carcinoma, around 8 skin cancer patient out of 10 have basal cell carcinoma. This type of skin cancer has a tendency to develop gradually and occurred due to UV radiation. Malignant melanoma is another type of cancer that can be developed from the melanocytes and melanocytes are the cell which contains pigment. Worldwide the main cause of skin cancer is exposure of UV radiation on skin and some antihypertensive drugs have the potential to cause carcinogen as they have the ability to absorb UV radiation directly from sun thus act as photosensitizing agent. For the progression of different type of cancer adiponectin which is a type of cytokine released from adipose tissue, take an important place. Late reviews have shown that low serum and plasma adiponectin levels in patients with RCC (Renal cell carcinoma) are related with a forceful phenotype and metastasis. Moreover, preclinical reviews have exhibited that exogenous adiponectin is fit for regulating cell expansion and apoptosis in different natural procedures, including tumor advancement (Ito et al., 2017). Several report on the basis of study said that antihypertensive drugs has capability to inhibit the progression of cell cycle and also proliferation of cell cycle as a result inhibit the apoptosis process. In United States, several case control study is done which proved the association of antihypertensive drugs with the increased rate of pancreatic cancer (Marie C. Bradley, 2010). Antihypertensive medication is widely used in the developed countries. Thus, any effects these drugs might have on prostate cancer risk are likely to have public health relevance (Linda Perron, 2004).

4.3.1 ACE inhibitors

In our study, we found that only lisinopril among all ACE inhibitors are associated with the risk of cancer. For lisinopril the number of report for neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant is higher than others. The numbers of reports are high for breast cancer than others. In the treatment of heart failure, management of renal insufficiency is really important to reduce the mortality rate and ACE inhibitors are most commonly used therapeutic agent in this case. To reduce the mortality rate due to heart failure ACE inhibitors is a standard medication which is proved by major studies. But again the possibility of adverse drug reactions is high among these patients. When we saw different study about the relationship among ACE inhibitors and cancer, we found some neutral effect. Some study said about their relationship but some are not. ACE inhibitors was not related with significant increase of

basal cell carcinoma, squamous cell skin carcinoma and malignant melanoma when the drug is used for short time but if these drugs are used for a longer period of time there is a chance for the occurrence of malignant melanoma. Some study said that ACE inhibitors reduce the risk of cancer among patients but when other study done to prove this evidence they failed which means ACE inhibitors do not reduce the risk of cancer. ACE inhibitors have a higher risk for the occurrence of cancer around 50% of patients. For the progression of different type of cancer, adiponectin which is a type of cytokine released from adipose tissue, take an important place. Late reviews have shown that low serum and plasma adiponectin levels in patients with RCC are related with a forceful phenotype and metastasis. Antihypertensive drugs supposed to decrease this amount of production of adiponectin but some antihypertensive drugs do not decrease this production for example lisinopril. In case of lisinopril, Study show that plasma concentrations of adiponectin do not change but increase the LDL cholesterol which may lead to breast cancer (Yilmaz et al., 2007). ACE inhibitors also show some other types of cancer but the amount of report is low than neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant. The others types of cancers which are reported in small number are bladder cancer, colon cancer, skin cancer etc.

4.3.2 Beta-blockers

In our study, we found that only metoprolol is associated with the risk of cancer. For metoprolol the number of report for neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant is higher than others. High intensity and long term use of beta blocker has the potency to cause malignant melanoma but low intensity beta blocker has the ability to occur squamous cell skin carcinoma for using short period of time. Utilization of beta blockers was related with high risk of breast cancer and this high risk is mainly observed in case of those patients who are used this drugs for a long period of time. In the management of heart failure and reduce the mortality rate beta blocker is useful. In case of young patient, the first line drug for hypertension is beta blocker (Ong, 2007). A case control study among the people of Australia proved undoubtedly about the occurrence of kidney cancer and pelvic cancer after using beta blocker. Study show that, in case of metoprolol plasma concentrations of adiponectin do not change but increase the LDL cholesterol which may lead to breast cancer (Yilmaz et al., 2007). This can be the reason for high amount of report for breast cancer in case of metoprolol. Beta

blockers also show some other types of cancer but the amount of report is low than neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant. The others types of cancers which are reported in small number are bladder cancer, colon cancer, skin cancer etc.

4.3.3 Calcium Channel Blockers

In our study, we found that only amlodipine among all ACE inhibitors are associated with the risk of cancer. For amlodipine the number of report for neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant is higher than others. The numbers of reports are high for breast cancer than others. At first, in 1996, Pahor et al., found that in patients who had took CCBs were in the high risk of breast cancer (W. Li et al., 2014). Recently some study said about the association between these agents and malignancy. So some study in large group and some trial were done to prove this association between calcium channel blocker with cancer. In some study this result was positive but in another the result was negative but some study said that calcium channel blocker has the positive result on breast cancer because these agents have the potential to inhibit the apoptosis process and thus lead to cancer. The effect of calcium channel blocker on skin cancer is weak. Again, epidemiologic evidence showed that there is a possibility for the association between utilization of calcium channel blockers and breast carcinoma. Some researchers said that calcium channel blocker is responsible for breast cancer but some other types can also cause this cancer. According to our pharmacovigilance study, we found that for CCBs the cases for breast cancer is high in number which proves that the previous study is true. The numbers of reports for skin cancer for all the CCBs are low which also proves that the study which was done before is completely accurate. On the other hand, nifedipine–a CCB- has been found to increase proliferation and migration of breast cancer cells, which could be responsible for the association between CCBs and late stage cancers. Again calcium channel blockers has also the potential to occur breast cancer because this drugs can inhibit the cell apoptosis process after effect influence the synthesis and metabolism of insulin (Babette S. Saltzman, 2013). This nifedipine effect–which is not shared by other CCBs such as verapamil seems to be produced via the Erk pathway activation and is independent of the calcium channel-blocking effect. Again, for nifedipine and amlodipine the occurrence of malignant neoplasm is higher in number. But prostate cancer, lung neoplasm malignant,

gastric cancer these all are only high in number for amlodipine. CCBs are also show some other types of cancer but the amount of report is low than neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant. The others types of cancers which are reported in small number are bladder cancer, colon cancer, skin cancer etc.

4.3.4 Diuretics

The result of our study reveals that only thiazide among all diuretics are associated with the risk of cancer. We mainly work with furosemide, bumetanide, metolazone and torasemide. But many studies are done to prove about the relationship between the use of diuretics and risk of cancer. One of the primary reviews proposing that diuretic treatment may be related with renal cell carcinoma originated from some interviewed based study. This interview revealed that cancer is a risk factor for diuretic only in women. Later on in a population based case control study proved that among women renal cell carcinoma is common due to using diuretics, not men. Again, after these studies researchers wanted to know more about the relationship between diuretics and antihypertensive drugs. They all got positive result about the association between them and the affected people are generally the long term user of antihypertensive drugs. Long term diuretics use has the potential to increase squamous cell carcinoma but no risk of basal cell carcinoma or malignant melanoma. Utilization of thiazide was related with modest chance of breast carcinoma. Further, long term utilization of these sorts of diuretics was related with high risk of breast carcinoma. A study was done in Seattle–Puget Sound metropolitan area among women of 65–79 years and reported that both short and long durations of use of these types of diuretics were associated with increased risks of breast carcinoma (C. I. Li et al., 2003). A diuretic especially thiazide diuretics is used for the primary treatment of hypertension and it has the ability to increase the risk of renal carcinomas (Keith T. Flaherty1, 2005). Thiazides are also show some other types of cancer but the amount of report is low than neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant. The others types of cancers which are reported in small number are bladder cancer, colon cancer, skin cancer etc.

4.3.5 Angiotensin II receptor blockers

The result of our study reveals that only valsartan among all ARBs are associated with the risk of cancer. We mainly work with losartan, valsartan, eprosartan and irbesartan. The result is positive for valsartan because the PRR value is moderately high for this

drug. For valsartan the number of report for neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant is higher than others. Many studies are done to prove about the relationship between the use of ARBs and risk of cancer. Angiotensin II receptor blockers are the primarily given successful drugs for hypertension patients and patients who are intolerance with this inhibitors will get benefit in several heart disease for example stable coronary heart disease . Angiotensin-receptor blockers (ARBs) are used widely as an antihypertensive drug and at first approved in 1995 for clinical purpose. Losartan is the first discovered drug as ARBs. The tolerability is proven good and effective in case of Angiotensin II receptor blockers and around 25% of patients suffering from hypertension are taking this drug worldwide. A clinical study in 2014 and CHARM-Overall study, LIFE study, ONTARGET and TRANSCEND studies, VALIANT studies prove the association of cancer due to using Angiotensin II receptor blockers (Dezsi, 2014). But according to research database of UK they did not get any evidence about their association in a large amount but they detect small risk about the breast and prostate cancer among the patients (Bhaskaran et al., 2012). A meta-analysis was done to determine the association of antihypertensive drugs and cancer which reported about the highly risk for the occurrence of cancer. Here, they found mainly the occurrence of liver cancer in increased rate. But the mechanism for this type of association is still unknown (Sipahi, Debanne, Rowland, Simon, & Fang, 2010). In our result, we found that other ARBs, except valsartan, are also show some other types of cancer but the amount of report is low than neoplasm malignant, breast cancer, prostate cancer and lung neoplasm malignant. The others types of cancers which are reported in small number are bladder cancer, colon cancer, skin cancer etc.

4.4 Susceptibility to cancer due to using antihypertensive drugs between male and female

The ADR in case of antihypertensive drugs are higher for female than male. . Previously several study report that the risk for women is 3 to 4 fold high comparing with men (Heck et al., 2010). Among all cancer skin cancer is common in case of using antihypertensive drugs and this is more common in case of women than men. Because, Skin is the cells in which the arrangement is integrated, complex that control several function and these functions are done by different layers of skin. Among all layers dermis is one and the thickness of the skin is depending on this layer. This thickness is

different for men and women. The thickness is lower in women comparing with men and this thickness is begins to decrease after the age of 45 and aftereffect of menopause this decrease 10 % thinner. So, the absorption of UV light is higher in women than men due to the thickness of skin of women. Melanin is the key component for the color of skin and the synthesized component from melanin is melanocytes. The distribution of melanocytes is different for individuals. Among the ethnic group of individual this may vary for example in ethnic groups the skin color of men is darker than women. Again the metabolism pattern of men and women are different. This all reasons are responsible for the higher occurrence of cancer in women. Again the use of tanning bed is increasing among women which may lead to cancer in women (Roh, Eliades, Gupta, Grant-Kels, & Tsao, 2017). Every year new cases for skin cancer are coming comparing with other type of cancer and the increasing rate for non-melanoma skin cancer (NMSC) among women 2 to 3 million. This increasing rate is for those women whose age is less than 45 years. Despite the fact that analysis and treatment of skin disease has negative mental impacts to any individual, contemplates demonstrate that women are influenced more than men, particularly youthful, single ladies who are especially worried about their wellbeing and appearance amid this time in their life. High anxiety, low quality of life, self-perception disappointment, and dread of repeat are among the consequences experienced by ladies who get a determination of melanoma or non-melanoma skin disease (Al-Dujaili, Henry, Dorizas, & Sadick, 2017). The risk for the occurrence of cancer is expanded among the people who are tall. Study of National Health Service (NHS) of UK found that the risk of cancer for tall women is more than others. The risk of pancreatic cancer in case of women for using antihypertensive drugs is lower than men which are reported by several investigators. The reason behind this is the hormones of female that reduce the pancreatic cancer risk in women. In the course of recent years numerous nations have encountered a dramatic ascent in the increased rate of thyroid cancer. With a review among five continents demonstrating that due to using antihypertensive drugs the rate is 67% for female and for male the rate is 48% between the years of 1973-2002 (Peterson, De, & Nuttall, 2012). Thyroid cancer which is a cancer of hormone dependent has some variation between male and female. In a study in England from 1962 to 1984 the occurrence of thyroid cancer increases in number. Thyroid cancer began rise at the age of 10 in case of female but for male the age is 18. The death of male due to thyroid cancer is occurred in earlier stage mentioned by occasional reports. To prove this a study is done by using the data 1994 to 2006 in Germany which give positive result between

difference among male and female in terms of thyroid cancer. Sporadic papillary thyroid cancers, sporadic follicular cancers, extra thyroidal extension of sporadic medullary cancers are significantly higher in male than female. But the rate of distant metastases from sporadic medullary cancers is higher is case of female (Machens, Hauptmann, & Dralle, 2006). But in case of colorectal cancer the rate of cancer occurrence is high for male than female due to the function of estrogen (Honma et al., 2011). According to the data of New Cross Hospital, Wolverhampton from 1989 to 2008, a study was done which proved that the risk of colorectal cancer is higher in female than male (Hebbar, Fuggle, Nevill, & Veitch, 2012). A study was done in New York State to estimate the incidence of cancer. They reported that they found the increased rate of liver and colorectal cancer among male than female. But the risk of thyroid cancer is higher in women than men (Ying Wang, 2002). The risk of lung cancer is not same for both men and women. The risk of lung cancer depends on the hormonal factors. The risk of lung cancer is higher in women than men. From the data of Shanghai Cancer Registry (SCR) a study was done to detect the risk of cancer which proved that the changing hormonal and ovarian properties affect the lung cancer. Regarding the risk of colorectal cancer, 1 concentrate revealed a risk lessening of 21% when contrasting beta blocker clients and clients of diuretics (Jansen, Below, Chang-Claude, Brenner, & Hoffmeister, 2012). A population based as well as statistical study was done in Denmark among 335682 people to show the relationship between the use of antihypertensive drugs and cancer. This study proves about the association between antihypertensive drugs and cancer risk. For this study, they used several classes of antihypertensive drugs. They found that the result is positive In case of diuretics, ACE inhibitors, beta blockers, calcium antagonists among the people who were 30 to 85 years old (Fryzek et al., 2005). A cohort study was done among the people of North Karelia, Finland to find the relation of incidence of cancer with hypertension. Here, they take women and men of mean age. For women the age was 58 and for men this was 51. They found that the risk of cancer for women is due to their high blood pressure and use of antihypertensive drugs. But they found that the rate is higher in men not only for antihypertensive drugs but also due to some additional reason like smoking (A. Lindgren, Pukkala, Tuomilehto, & Nissinen, 2007).

4.4.1 ACE inhibitors

To begin with, ACE inhibitors are the drugs which are more susceptible to female than male. Like, except enalapril all the drugs of ACE inhibitors which we choose have the ability to occur more in female than male. As, for female the percentage of with lisinopril, captopril, quinapril and ramipril is greater than 50 which prove that female is more susceptible to cancer than men.

4.4.2 Beta blockers

Again, for beta blockers, female are more susceptible to the risk of cancer than male because for maximum drugs the numbers of reports are higher for female. Other than bisoprolol, the rate is high for female. In case of betaxolol, 100% report is found only for female as the reports which reported are only for female.

4.4.3 Calcium Channel Blockers and diuretics

Further, the number of reports came for calcium channel blockers and diuretics are almost equal for all the drugs. Like, in case of CCBs, for amlodipine and felodipine the rate of reports are higher for male. On the contrary, for other two drugs, verapamil and nifedipine, the number of reports are high for female. Again, in case of diuretics, the numbers of reports for furosemide as well as metolazone are high for female and the numbers of reports for bumetanide as well as torasemide are high for male.

4.4.4 Angiotensin II receptor blockers

According to the outcome of our study we found that the risk of cancer in case of angiotensin II receptor blockers is higher for female for all the drugs. As, for all the drugs, the number of reports come for female is more than 50% for female.

CHAPTER FIVE

CONCLUSION

Chapter 5: Conclusion

To sum up, we conducted a pharmacovigilance study by extracting the data from VigiAccess database. The data conferred in this study indicated that several antihypertensive drugs, which categorized to the group of ACE inhibitors, beta blockers, Angiotensin II receptor blockers, calcium channel blockers and diuretics, are moderately related with cancer risk as an ADR. These are also associated with the risk of developing new cancer like different types of neoplasms. For some drug the amount of reports are so high that prove without any doubt that this drug is definitely associated with cancer. To illustrate, lisinopril, metoprolol, amlodipine and valsartan are associated with risk of cancer. Again, in this pharmacovigilance study, we found that there are also some drugs in which the numbers of reports are really low but they show their association with cancer like quinapril. Furthermore, all the drugs of same group are not associated with this risk. To include, all the drugs of several groups are not shown the risk of cancer and their reports are also really low. Not only this study outcome but also many study proves that some antihypertensive drugs are responsible for cancer. If we attempt to draw a conclusion by showing the outcome of this pharmacovigilance study, it will be clear about the significance of only few antihypertensive drugs which need considerable attention.

In this study, total four drugs show their correlation with cancer and these are from different groups like lisinopril, amlodipine, quinapril and metoprolol. The outcome of our study shows that increasing the number of reports increases their tendency to show the positive result. Among all the ACE inhibitors only lisinopril and quinapril show their association with cancer. Again, from all the Angiotensin II receptor blockers solely valsartan has the link with cancer and none other drugs are not linked with cancer. Further, diuretics are not responsible for the occurrence of cancer as an ADR. Furthermore, Amlodipine is the only drug among all calcium channel blockers which is associated with cancer risk.

Our study demonstrate that, patients who are taking some specific antihypertensive drugs, like lisinopril, amlodipine, quinapril and metoprolol, for a long period of time are mainly in the increased risk for the incident of neoplasm malignant, breast cancer and prostate cancer. The incidence of lung neoplasm malignant, bladder cancer and skin cancer are also high in amount. Again different types of cancer like throat cancer, renal

cancer, gastric cancer, colon cancer etc. can occur due to using antihypertensive drugs though the number is low but there is possibility to occur. Our study also suggests the occurrence of new cancer due to using lisinopril, amlodipine, quinapril and metoprolol. This is because the occurrence of neoplasm is also high in number for these drugs.

At last, in our study we suggest that female are more susceptible to cancer due to using antihypertensive drugs than male. For ACE inhibitors, beta blockers and angiotensin II receptor blockers female are more susceptible to cancer after using antihypertensive drugs. But for diuretics and calcium channel blockers this rate is almost equal for male and female.

CHAPTER SIX

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Chapter 6: Reference

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