*ejpmr, 2019,6(4), 396-403*

**SJIF Impact Factor 4.897**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

**Research Article**

**ISSN 2394-3211**

**EJPMR**

# ANTI HYPERTENSIVE DRUGS FOR PULMONARY ARTERIAL HYPERTENSION (PAH) IN INTERNATIONAL PHARMACOVIGILANCE: DATA MINING STUDY

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**Article Received on 31/01/2019** **Article Revised on 20/02/2019** **Article Accepted on 12/03/2019**

## ABSTRACT

Precapillary pulmonary hypertension with a mean pulmonary artery pressure of >25 mm Hg and a normal pulmonary artery wedge pressure of <15mmhg is pulmonary arterial hypertension signs and symptoms of PAH are similar to those of heart & lung conditions. The prevalence of PAH is thought to be range of 15-50 subjects per million population in Europe. Biological factors, chemical factors genetical factors are the confounding risk factors for PAH drug use PAH can be associated with exposure to certain drugs or toxins, particularly to appetite suppressant intake drugs. PAH is a disease of precapillary pulmonary arterial bed, including the medium sized pulmonary arteries &pulmonary arteriols characterized by vascular obliteration widespread endothelial apoptosis result in proliferation of apoptosis resistant endothelial precursor cell & that proliferate & eventually form plexiform lessions PAH has a genetic component. The bone morphogenetic proteins (BMP) are part of the transforming growth factor superfamily (TGF-BETA). The disfunctional pulmonary hypertensive endothelial cell phenotype is characterized by uncontrolled proliferation increased production of vasoconstrictor mediators such as endothelin expression of 5-lipoxygenase & decreased synthesis of prostacyclin $CCB_S$, $ERA_S$,PD5 inhibitors, guanylate cyclase stimulators, prostacyclin IP receptors agonists are used for treatment of PAH.

**KEYWORDS:**

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is defined by right-heart catheterization (RHC) showing precapillary pulmonary hypertension with a mean pulmonary artery pressure (mPAP) of >25 mmHg and a normal pulmonary artery wedge pressure (PCWP) of <15 mmHg.[1]

## SIGNS

Many of the signs and symptoms of PAH are similar to those of other heart and lung conditions. These symptoms may include shortness of breath, dizziness or fainting, racing pulse or heart palpitations, fatigue, weakness, chest pain and cough which makes it difficult to notice abdominal swelling, or swelling of the arms, legs, or ankles blue or chalky skin, especially at the fingertips.

## MATERIALS AND METHODS

## REASONS

Sometimes doctors can't find a reason for high blood pressure in the lungs. In that case, the condition is called idiopathic pulmonary hypertension. Genes may play a role in why some people get it. In other cases, another condition causing the problem. Any of these illnesses can lead to high blood pressure.

## EPIDEMEOLOGY

The annual rate of PAH has been estimated to be 2.4 cases per million people per year in France and 7.1~7.6 cases per million population per year in Scotland.[2,3] The prevalence of PAH is 5~25 cases per million people in France and 26~52 cases per million population in Scotland. Therefore, the prevalence of PAH is thought to be in the range 15-50 subjects per million population in Europe. In the French registry, 39.2% of patients diagnosed with PAH had IPAH and 3.9% had family history. Besides, 9.5% had anorexigen exposure, 15.3% had CTD (mainly SSc), 6.2% had HIV infection, 10.4% had portal hypertension, and 11.3% had CHD. In the REVEAL registry conducted in US, half of enrolled patients (50.7%) presented with APAH and 46.2% were IPAH In the subgroup of APAH, CTD, CHD, portal hypertension, drugs/toxins and HIV infection corresponded to 49.9, 19.5, 10.6, 10.5, and 4.0% of the people, respectively.[6-11]

## RISK FACTORS

Anyone can develop PAH. There are a number of risk factors that can make someone more susceptible to this and other heart and lung conditions, such as The mean

age at presentation was 36 ± 15 years and the majority of the patients were females.

**BIOLOGICAL FACTORS**

Smooth muscle contraction occurs by influx of calcium either through voltage gated ion channels, Ionositol 1, 4, 5-tri phosphate (IP3) mediated receptors on sarcoplasmic endoplasmic reticulum or by Phosphokinase c (PKC). When a ligand binds to GPCR receptor it activates phospholipase C, which converts ionositol 4, 5 bis phosphate (PIP2) to IP3. IP3 binds to IP3 receptors thus causing efflux of calcium into endoplasm. Also PLC activates DAG, which activates PKC thus causing influx of calcium into endoplasm. Prostaglandins act on prostanoid receptors which are kinase type receptors activate PLC thus activating DAG, and causing calcium influx. Calcium acts on calmodulin thus activating myosin light chain kinases (MLCK) which phosphorylates myosin thus actin-myosin filaments bind causing contraction.

**CHEMICAL FACTORS**

Cellular and molecular mechanisms responsible for the pathobiology of PAH. This summary aims to present the current state of our understanding of some of the key mechanisms. We also indicate further areas and directions of research and suggest novel approaches to therapy.

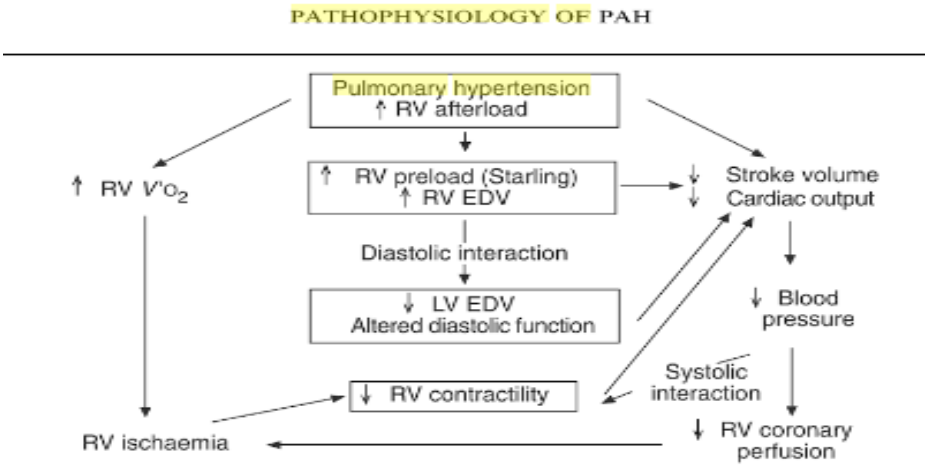
**GENETICAL FACTORS**

Pulmonary arterial hypertension may be heritable (HPAH), idiopathic, or associated with drug or toxin exposures (fenfluramine derivatives or toxic oil syndrome), or other medical conditions, including connective tissue diseases, human immunodeficiency virus infection, congenital heart disease, and portal hypertension bone morphogenetic protein receptor type 2 (*BMPR2*) was identified following linkage analysis as the gene responsible for more than 70% of HPAH and approximately 20% of IPAH cases. Two further receptor members of the transforming growth factor (TGF)-β cell signaling super family are also recognized as uncommon causes of HPAH. Heterozygous mutations in activin-like kinase-type 1 (*ALK1*) and endoglin (*ENG*) cause hereditary hemorrhagic telangiectasia (HHT) and may rarely lead directly to the development of PAH.[12]

**Tab.1: Genetic Factors.**

| Genes | Mutation |
|---|---|
| ALK1 | ACVRL1 mutation carriers had better hemodynamic status at diagnosis, but none responded to acute vasodilator challenge and they had shorter survival when compared with other patients with PAH despite similar use of specific therapies. |
| ENG9 (Endoglin) | All research conducted in *ENG*gene have been performed in IPAH or HPAH patients, but the study by Pfarr et al described a small number of pathogenic mutations in patients with congenital heart disease associated to PAH. |
| BMPR2 & SMAD9 | BMPR2and SMAD9. One non-canonical function of BMP signaling regulates biogenesis of a subset of micro RNAs. We have previously shown that this function is abrogated in patients with HPAH, making it a highly sensitive readout of BMP pathway integrity. |
| CAV(caveolin) | we identify a Heterozygous F160X CAV1 mutation predicted to generate a C-terminally truncated mutant protein in a patient with both PAH and CGL using whole exome sequencing, and characterize the properties of CAV1 |
| KCNK3 | Robust gene expression of *KCNK3*in healthy and familial PAH patient lungs, but no quantifiable expression of *KCNK9*, and demonstrated in functional studies that KCNK9 minimizes the impact of select KCNK3 mutations when the 2 channel subunits co-assemble. |

**PATHOPHYSIOLOGY**



**Complications of PAH**

- Sudden cardiac death.
- Pleural effusions.
- Gross peripheral oedema.
- Exertional syncope.
- Deteriorating right heart function and right-sided cardiac failure.
- Hepatic congestion and cardiac cirrhosis.
- Gross exertional dyspnoea.
- Problems during childbirth, including sudden death.

**TREATMENTS**

**Tab.2: Classes of drugs.**

| Classes | Drugs |
|---|---|
| **Class 1** | Ambrisentan,bosentan,macitentan |
| **Class 2** | Ambrisentan, bosentan, macitentan, riociguat, sildenafil, tadalafil. |
| **Class 3** | Ambrisentan, bosentan, epoprostenol, iloprostinhaled, macitentan, riociguat, sildenafil, tedalafil, treprostinil. |
| **Class 4** | Epoprostenol, ambrisentan, bosentan, iloprost, inhaled&i.v, macitentan, riociguat, sildenafil, tadalafil, treprostinil. |

**CLASSES OF TREATMENT**

Classes of drugs.

**Tab.3: Classes of Treatment**

| **Drugs used for treatment of pulmonary arterial hypertension (group 1)** | **Comment** |
|---|---|
| Calcium channel blockers | e.g., Amlodipine |
| Endothelin receptor antagonist | Ambrisentan |
| | Bosentan |
| | Macitentan |
| Phosphodiesterase type 5 inhibitors ( no pathway) | Sildenafil<br>tadalafil |
| Guanylate cyclase stimulators (no pathway) | Riociguat |
| Prostacyclin analogues | Epoprostinol (intravenous) |
| | Iloprost 9inhaled0 |
| | Treprostinil (subcutaneous) |
| Prostacyclin ip receptor agonists | Selexipag (oral) |

**GROUP 1 PAH therapy**

**Tab.4: GROUP 1 PAH therapy**

| Recommendations for efficacy of specific drug therapy, ballon atrial septostomy, and lung transplantation(group 1) according to who functional class (WHO-FC) | | | | |
|---|---|---|---|---|
| **Measurement** | | **Classes of Recommendation-Level Of Evidence** | | |
| | | WHO-FC II | WHO-FC III | |
| Calcium channel blockers | I-c[a] | I-c[a] | .. | |
| Endothelin receptor antagonist | Ambrisentan<br>Bosentan<br>Setaxentan | I-A<br>I-A<br>$II_a$-C | I-A<br>I-A<br>I-A | $II_a$ - C<br>$II_a$ - C<br>$II_a$ - C |
| Phosphodiesterase type 5 inhibitors | Sildenafil | I-A | I-A | $II_a$- C |
| | Tadalafil | I-B | I-B | $II_a$- C |
| Protanoids | Beraprost | -- | Ib-B | -- |
| | Epoprostinol (intravenous) | -- | I-A | I-A |
| | Iloprost (inhaled) | -- | I-A | $II_a$-C |
| | Iloprost (intravenous) | -- | $II_a$-C | $II_a$- C |
| | Treprostenil (subcutaneous) | -- | I-B | $II_a$- C |
| | Treprostenil (intravenous) | -- | $II_a$-C | $II_a$- C |
| | Treprostenil (inhaled) | -- | I-B | $II_a$- C |
| Initial drugs combination | -- | -- | -- | $II_a$ - C |

| | | | | |
|---|---|---|---|---|
| therapy | | | | |
| Sequential drugs combination therapy | -- | $II_a$- C | $II_a$ - B | $II_a$-B |
| Balloon arterial septostomy | -- | -- | I-C | I-C |
| Lung transplantation | -- | -- | I-C | I-C |

The Drugs used for Data mining are Ambrisentan, Bosentan and Macitentan.

## RESULTS AND DISCUSSION

After the pharmacovigilance study the percentage of side effects were decreases compared to previous the study was done from 2002 -2018 in between 2015-1017 the cases was in decreased manner. PAH is a rare disorder of which very little is known. The number of patients suffering from PAH is raising from day to day due to increase in co-morbidity that causes PAH. The mean age was 36 (+or-) 15 years and as we can see most the patients are females. The exact cause is still unknown. Mostly PAH occurs due to genetical mutations with BMPR2 responsible for 70% HPAH & approximately 20% of IPAH cases. BMPR2 mutations cause up regulation/down regulation of mutated micro RNAS which causes abnormal BMP pathway function. We can't rule out only BMPR2 is responsible for PAH but also other genes such as ALK1, ENG9 etc..Chemical/biological factors are secondary to genetical but PAH is not precipitated due to chemical/biological there are very rare cases of irreversible PAH in patients who have been under the treatment of fenfluramine, aminorex, antivirals can cause PAH.

**Tab 5: Number of Individual Cases By Age Group (WHO-UMC).**

| Age group | Ambrisentan | | Bosentan | | Macitentan | |
|---|---|---|---|---|---|---|
| | Cases | % | Cases | % | Cases | % |
| 0-27 days | 1 | 0 | 12 | 0 | 5 | 0 |
| 28days-23months | 31 | 0 | 447 | 1 | 7 | 0 |
| 2-11years | 448 | 1 | 642 | 2 | 20 | 0 |
| 12-17years | 459 | 1 | 292 | 1 | 59 | 0 |
| 18-44years | 6328 | 10 | 2455 | 8 | 1340 | 11 |
| 45-64years | 18587 | 29 | 6523 | 21 | 3965 | 34 |
| 65-74years | 12296 | 19 | 4936 | 16 | 3311 | 28 |
| >75years | 10185 | 16 | 4899 | 16 | 2736 | 23 |
| Not specified | 16202 | 25 | 10331 | 34 | 3850 | 3 |

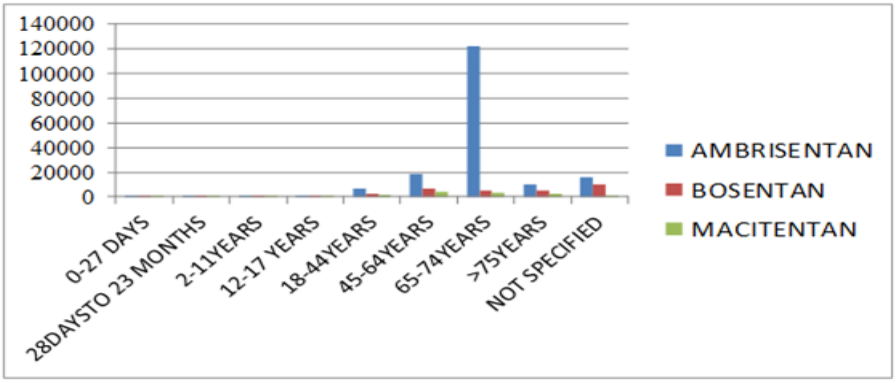



**Fig.1: Graph of Individual Cases by Age (WHO-UMC).**

**Tab 6: Number of Individual Cases by Age (Eudravigilance).**

| Age Group | AMBRISENTAN | | BOSENTAN | | MACITENTAN | |
|---|---|---|---|---|---|---|
| | Cases | % | Cases | % | Cases | % |
| 0-1 months | 7 | 0.00 | 10 | 0.10 | 4 | 0.10 |
| 2months | 17 | 0.10 | 254 | 2.60 | 8 | 0.20 |
| 3-11years | 105 | 0.50 | 197 | 2.00 | 5 | 0.10 |
| 12-17years | 154 | 0.70 | 188 | 1.90 | 26 | 0.60 |
| 18-64years | 8998 | 43.50 | 3704 | 37.90 | 1916 | 45.10 |
| 65-86years | 8255 | 39.90 | 3217 | 32.90 | 1930 | 45.40 |
| >85years | 728 | 3.50 | 338 | 3.50 | 185 | 4.40 |
| Not specified | 2434 | 11.80 | 1862 | 19.10 | 175 | 4.10 |

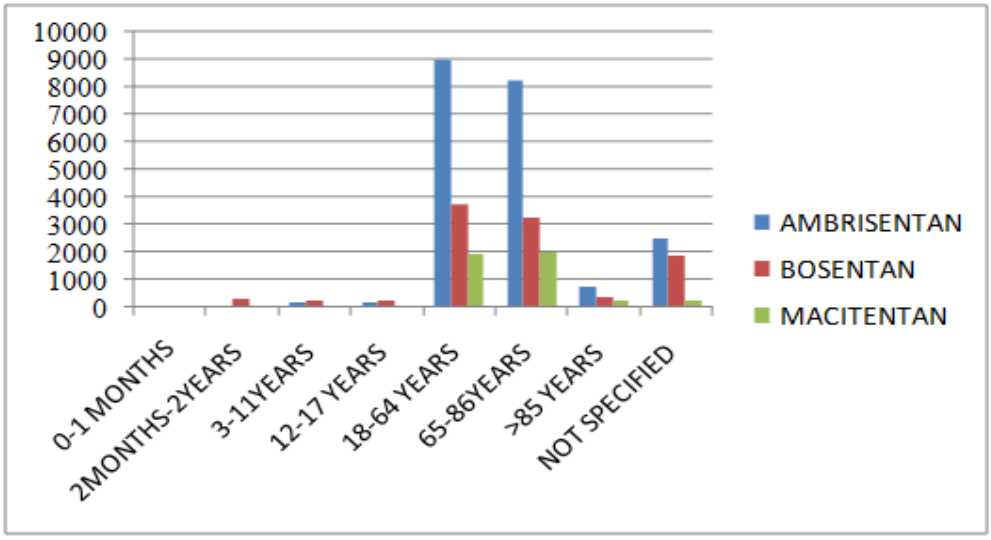



**Fig.2: Graph of Individual Cases by Age (Eudravigilance)**

**Tab.7: Number of Individual Cases By Gender (WHO-UMC)**

| Gender | Ambrisentan | | Bosentan | | Macitentan | |
|---|---|---|---|---|---|---|
| | Cases | % | Cases | % | Cases | % |
| Female | 48405 | 75 | 15752 | 52 | 8690 | 73 |
| Male | 15662 | 24 | 5641 | 18 | 3021 | 26 |
| Not specified | 470 | 1 | 9144 | 30 | 117 | 1 |

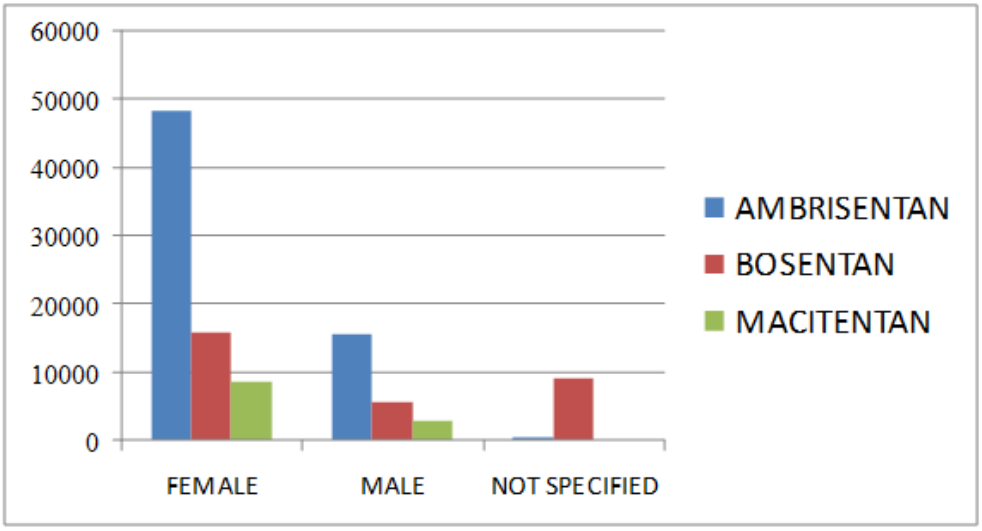



**Fig.3: Graph Of Individual Cases By Gender(WHO-UMC).**

**Tab.8: Number of Individual Cases by Gender (Eudravigilance)**

| Gender | AMBRISENTAN | | BOSENTAN | | MACITENTAN | |
|---|---|---|---|---|---|---|
| | Cases | % | Cases | % | Cases | % |
| Female | 13700 | 66.20 | 5744 | 58.80 | 2980 | 70.10 |
| Male | 4864 | 23.50 | 2390 | 24.50 | 1187 | 27.90 |
| Not specified | 2134 | 10.30 | 1636 | 16.70 | 83 | 2.00 |

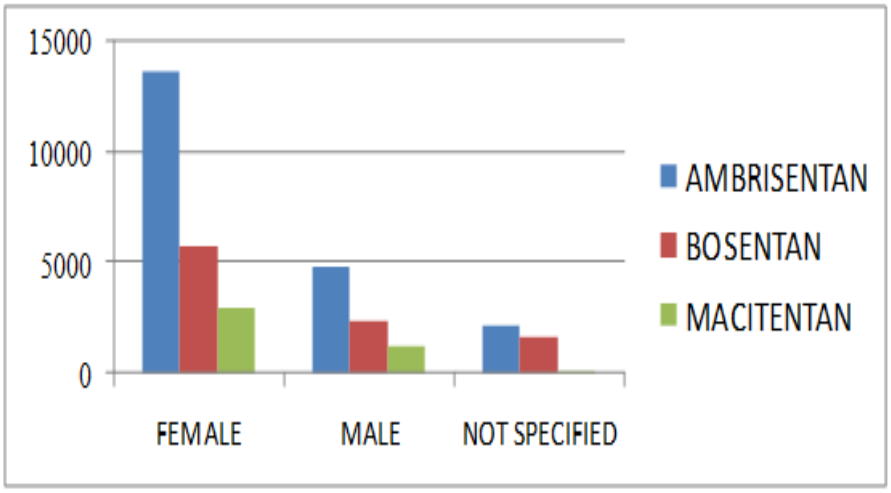



**Fig.4: Graph of Individual Cases by Gender (Eudravigilance)**

**Tab.9: Number of Individual Cases by Year**

| Year | Ambrisentan | | Bosentan | | Macitentan | |
|---|---|---|---|---|---|---|
| | Cases | % | Cases | % | Cases | % |
| 2018 | 1989 | 3 | 411 | 1 | - | 8 |
| 2017 | 6996 | 11 | 2189 | 7 | - | 33 |
| 2016 | 5275 | 8 | 2197 | 7 | - | 24 |
| 2015 | 21917 | 34 | 4767 | 16 | - | 34 |
| 2014 | 19353 | 30 | 4280 | 14 | - | 2 |
| 2013 | 1405 | 2 | 1621 | 5 | - | 0 |
| 2012 | 3085 | 5 | 3833 | 13 | - | 0 |
| 2011 | 2616 | 4 | 7427 | 4 | 945 | 0 |
| 2010 | 844 | 1 | 717 | 2 | 3849 | - |
| 2009 | 835 | 1 | 366 | 1 | 2786 | - |
| 2008 | 220 | 0 | 466 | 2 | 3997 | - |
| 2007 | 0 | 0 | 27 | 0 | 247 | - |
| 2006 | 2 | 2 | 326 | 1 | 0 | - |
| 2005 | - | - | 583 | 2 | 3 | - |
| 2004 | - | - | 832 | 3 | 1 | - |
| 2003 | - | - | 485 | 2 | 945 | - |
| 2002 | - | - | 10 | 0 | 3849 | - |

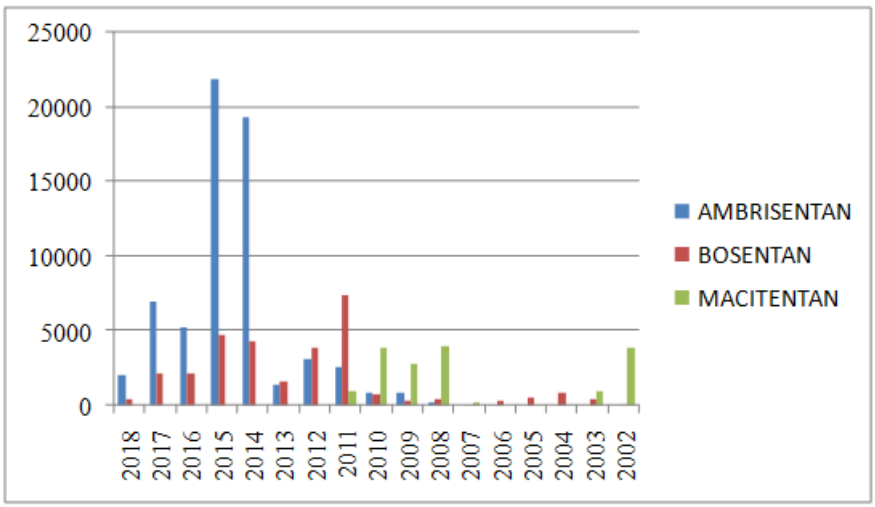



**Fig.5: Graph of Individual Cases by Yea.**

**Tab.10: Number of Individual Cases By Side Effects (WHO-UMC)**

| Side effects | Ambrisentan | Bosentan | Macitentan |
|---|---|---|---|
| Blood and lymphatic system disorders | 1436 | 1152 | 575 |
| Cardiac disorders | 5812 | 4338 | 1642 |
| Congenital,familial and genetic disorder | 176 | 166 | 51 |
| Ear and labyrinth disorder | 544 | 145 | 167 |
| Endocrine disorder | 86 | 88 | 40 |
| Eye disorder | 1185 | 360 | 276 |
| Gastrointestinal disorder | 7772 | 3733 | 2295 |
| General disorders and administration site condition | 25236 | 15112 | 5753 |
| HEPATOBILIARY DISORDER | 715 | 1347 | 247 |
| IMMUNE SYSTEM DISORDER | 733 | 283 | 178 |
| INFECTIONS AND INFESTATION | 10863 | 5181 | 2726 |
| Injury,poisoning and procedural complications | 4168 | 2668 | 1208 |
| Investigations | 6824 | 5433 | 2177 |
| Metabolism and nutrition disorder | 4847 | 2241 | 1425 |
| Musculoskeletal and connective tissue disorders | 4143 | 1732 | 1214 |
| Neoplasms begin, malignantand unspecified (incl cysts and polyps) | 960 | 869 | 294 |
| Nervous system disorders | 10383 | 3566 | 2318 |
| Pregnancy,puerperium and perinatal conditions | 56 | 194 | 22 |
| Product issues | 513 | 232 | 180 |
| Psychiatric disorders | 1784 | 888 | 563 |
| Renal and urinary disorders | 1644 | 1253 | 619 |
| Reproductive system and brest disorders | 280 | 179 | 116 |
| Respiratory,thoracic and mediastinal disorders | 19854 | 7891 | 4241 |
| Skin and subcutaneous tissue disorders | 2504 | 1018 | 696 |
| Social circumstances | 390 | 221 | 134 |
| Surgical and medical procedures | 3787 | 3888 | 1582 |
| Vascular disorders | 3849 | 1988 | 1111 |

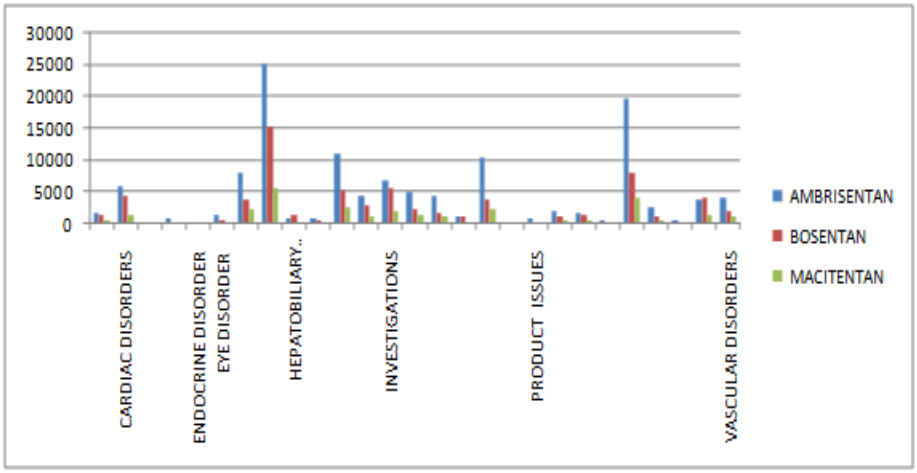



**Fig.6: Graph of Individual Cases By Side effects.**

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