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The Use of Ace Inhibitors and Angiotensin II Receptor Blockers in Hypertension and Associated Risk of Breast Cancer in Women

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Nursing 997

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Darla R. Danielson Anderson, RN, BSN, S-FNP

3/6/18

Abstract

The Joint National Committee (JNC-8) current guidelines recommend providers use angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) as first line medications for the treatment of hypertension. As with any medication, there are associated risks and benefits. A brief review of the literature found conflicting information in terms of what effect, if any, ACEI or ARB's have on breast cancer. Several studies have theorized that ACEI/ARBs may have anti-tumor properties, specifically in terms of breast cancer while other studies indicate an increased risk or no association with breast cancer.

A review of literature through the Harley French Library at the University of North Dakota was conducted to determine the risk versus benefits of ACEI/ARBs in relevance to breast cancer. Using the databases CINAHL and Pub Med, years 2012-2018, a search using the terms *ace inhibitors*, *angiotensin receptor blockers*, and *breast cancer* was ensued. A total of 167 articles were found through CINAHL, nine of them relevant to this topic. Pub Med revealed 57 total articles, two appropriate for use in this paper.

Developed from an Objective Structured Clinical Examination (OSCE) on the management of newly diagnosed hypertension in a 60-year-old female, the purpose of this literature review is to discover what, if any, cancer associated risk exist with the use of ACEI/ARBs.

The Use of Ace Inhibitors/Angiotensin II Receptor Blockers in Hypertension and Associated Risk of Breast Cancer in Women

In the United States, hypertension and breast cancer are high on the list of illnesses contributing to the morbidity/mortality of women. Overall, 1 in 3 Americans have hypertension, specifically after age 64 more women than men have hypertension (American Heart Association, 2013). Untreated, hypertension can lead to multiple conditions including myocardial infarction, heart failure, renal failure, loss of vision, stroke, and peripheral vascular disease (Woo & Robinson, 2016). Another commonly occurring disease affecting women is breast cancer. Breast cancer is listed as the most commonly occurring neoplastic disease and leading cause of cancer death among women (Chang et al., 2016; Raebel et al., 2017).

The Joint National Committee guidelines on hypertension management list angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) as first-line medications used in the treatment of hypertension (Woo & Robinson, 2016). In 2013 there were a combined 10+ million prescriptions for ACEI/ARBs filled in the United States alone, making these classes some of the most commonly prescribed medications (Delmare, 2015). As with any medication there are associated risks and benefits to their use. Initial research indicated a possible increased risk for development of breast cancer in women who use ACEI/ARBs for management of their hypertension. However, controversial data now exists in terms of an associated increased risk versus protective benefit against breast cancer in women who use these medications for the management of hypertension.

Developed from a family nurse practitioner Objective Structured Clinical Examination (OSCE) exam involving the management of newly diagnosed hypertension in a 60-year old woman, this paper reviews current literature to determine the risk versus benefits of ACEI/ARBs

and associated risk of breast cancer among women using these medications for the management of hypertension.

Case Report

XX is a 60-year old Caucasian female with a medical history significant for newly diagnosed hypertension who presented to the clinic for follow-up after starting lisinopril, an ACEI, 20 mg by mouth once daily three weeks ago. XX endorsed feeling well since starting lisinopril, however did report having developed a dry, non-productive cough. She denied having symptoms of upper respiratory illness such as fever, chills, sweats, sinus congestion, rhinorrhea, sore throat, shortness of breath, or chest pain associated with the cough. She also denied having headaches, dizziness, lightheadedness, or edema. XX stated she had been monitoring her blood pressures at home since starting lisinopril, finding them to consistently be 140/80's. Additionally, XX has made lifestyle changes including following a low salt, low fat diet along with incorporating exercise into her weekly routine. Other positive findings during review of systems with XX discovered occasional "heart burn" symptoms relieved with Tums. She denied having chest pressure/pain/discomfort, heaviness, palpitations, shortness of breath, nausea, vomiting, or other symptoms indicating acute coronary syndrome.

XX's family history is strong for cardiovascular disease with her sister and brother both diagnosed with hypertension; her father has had open heart surgery. XX endorsed having a personal 20 pack/year cigarette smoking history, a habit she quit 10 years ago. She is married, with adult children, and retired from the nursing profession. Current medications reported by patient include a daily multivitamin and lisinopril 20 mg by mouth once daily.

This clinic visit found XX to be afebrile, her blood pressure elevated at 160/98, pulse regular and strong at 80 beats per minute, respiratory rate of 20. XX's physical exam was

thoroughly negative for any concerning findings including wheezing, rales, irregular heart beat, skin changes, neurological deficits, or edema.

Many patients are unable to tolerate taking ACEI due to the development of a dry cough. This common side effect is thought to be associated with bradykinin, an anti-inflammatory, vasodilating mediator broken down into its active fragments by ACEI (Woo & Robinson, 2016). Angiotensin II receptor blockers have similar anti-hypertensive actions as ACEI (Woo & Robinson, 2016). Unlike ACEI, ARB's do not affect bradykinin nullifying the risk of the commonly ACEI associated cough (Woo & Robinson, 2016).

Given the review of systems and physical assessment findings, the cause of XX's cough is most likely this common side effect of lisinopril (Woo & Robinson, 2016). Following the JNC-8 guidelines, XX's cough can be easily remedied by changing the ACEI, lisinopril, to the ARB, losartan to continue appropriate management of her hypertension (Woo & Robinson, 2016).

When considering medication management for any disease process, it is imperative that health care providers consider patient risk factors, side effects and associated risks of the medications prescribed. While XX's past medical history is most significant for cardiovascular disease, her age and smoking history put her at risk for breast cancer as well. Plan of care for XX includes continued lifestyle changes, discontinuation of lisinopril, initiating losartan to manage hypertension, and routine health maintenance such as immunizations, osteoporosis, breast and colon cancer screening. A complete review of XX's OSCE can be found in Appendix A.

Pathophysiology

Blood pressure is regulated, in part, through the body's renin angiotensin system (RAS) (Chae et al., 2011; Woo & Robinson, 2016). The RAS system contains both angiotensin I and

angiotensin II receptors (Vinson, Barker, & Puddefoot, 2012). Angiotensin-converting enzymes change inactive angiotensin I into active angiotensin II, a key regulator in the secretion of aldosterone and thus salt/water retention and vascular tone (Lee et al., 2012; Napoleone et al., 2011). Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers reduce blood pressure through inhibition of vasoconstrictive angiotensin II and decreased production of aldosterone there by reducing the overall circulating intravascular volume (Chae et al., 2013; Woo & Robinson, 2016). Utilizing this understanding of RAS/cancer cell pathophysiology researchers aim to seek the potential benefits of ACEI/ARBs in cancer treatment. See Appendix B for complete RAS system pathophysiology.

In addition to decreasing hypertension, angiotensin-converting enzyme inhibitors offer renal protection, which is a benefit to diabetic patients with proteinuria (Woo & Robinson, 2016). Angiotensin II receptor blockers do not prevent diabetic nephropathy but do offer the benefit of slowing the progression of renal disease (Woo & Robinson, 2016). These antihypertensive medications also offer benefit to patients with congestive heart failure (Chae et al., 2013).

Breast cancer cells have been found to contain full components of the renin angiotensin system, showing signs of increased cancer cell proliferation and angiogenesis in the presence of angiotensin II (Chae et al., 2013; Vinson, Barker, & Puddefoot, 2012). Angiotensin II, among its' many actions, works as a growth factor in both normal and breast cancer epithelial cells (Chae et al., 2013; Lee et al., 2012; Napoleone et al., 2011). Angiotensin II regulation is also involved in programmed cell death, a key component in the treatment of cancer (Vinson, Barker, & Puddefoot, 2012). When both angiotensin I and II receptors are blocked, there is inhibition of

tumor cell proliferation, angiogenesis, and metastasis (Napoleone et al., 2011; Vinson, Barker, & Puddefoot, 2012).

Literature Review

The literature contains conflicting information in terms of what effect, if any, ACEI or ARB's have on breast cancer. Several studies have indicated that ACEI/ARBs may have anti-tumor properties, specifically in terms of breast cancer, while other studies indicate an increased risk or no association in the development of breast cancer. Multiple variables were noted throughout the studies in this literature review. When considering data obtained from any study, it is imperative that the results are based on consistent, reliable, and reproducible information and must consider confounding variables. Variables other than only the use of ACEI/ARBs such as age, gender, race, genetics, weight, smoking history, and socio-economic status should be considered when determining any positive or negative association with medication use and breast cancer. Ultimately, providers must weigh the benefits ACEI/ARBs provide in terms of hypertension management and risk reduction against the potential risks these classes of medication present when prescribing.

Associated Risk

Research and data have established the effectiveness of ACEI/ARBs in treating hypertension (Lonati & Morganti, 2014). Ganz, Habel, Weltzein, Caan, & Cole (2011) reviewed data from the 2000 Life After Cancer Epidemiology (LACE) study to determine risk between antihypertensive medications such as ACEI and breast cancer recurrence in women. Recognizing a wide array of modifiable and non-modifiable variables influence cancer development and recurrence, authors of this study found ACEI to cause a significant increased risk of breast cancer recurrence (HR=1.56, 95% CI, 1.02, 2.39).

Sorenson et al. (2013) corroborated the LACE data. Utilizing a prospective cohort study platform, seven years of data from 18,733 women with pre-diagnosed, non-metastatic breast cancer was reviewed. Looking specifically at the rate of breast cancer recurrence in the setting of previous ACEI-ARB use, researchers considered several confounding variables (age, menopause, cancer staging, etc.) in determining the study outcomes. Women who used ACEI were found to have a slightly increased risk of breast cancer recurrence (HR=1.2, 95% CI, 0.97-1.4) over those women who did not use ACEI. Additionally, researchers of this study determined ACEI/ARBs do not offer any protective benefit against cancer recurrence.

The MCC-Spain Study revealed slightly different data than Sorenson et al. and Ganz et al. found. This large, population-based case-control study reviewed 1,736 breast cancer cases, seeking to discover any association between the use of anti-hypertensive medications and breast cancer development (Gomez-Acebo et al., 2016). Researchers discovered an increased risk of breast cancer in premenopausal women who used ARBs for hypertension management (OR 4.27, 95% CI, 1.32-13.84). Conversely postmenopausal women were found to have no increased risk of breast cancer associated with the use of ACEI.

Sipahi et al. (2011) questioned what effect ACEI have on cancer occurrence and cancer death. In this large study, information from meta-analysis of 14 studies (range 23,291-61,744 participants) looked specifically at randomized control trials involving ACEI with mention of cancer occurrence. Findings from this large study indicate ACEI do not offer protective benefits against cancer or cancer related death. In contrast to other studies reviewed, data gathered in this study is not gender specific nor does it address menopausal status of any women in the study. Importantly, in terms of this author's review, data specific to breast cancer alone was not

reviewed; this study looked at generalized cancer occurrence and death. Furthermore, while ACEI were reviewed, ARBs were conspicuously absent from this meta-analysis.

Data collected by Song et al. (2017) found conflicting data. This meta-analysis reviewed PubMed, Embase, and the Cochrane Library, ultimately selecting 11 studies with a total of 4,964 participants. Their research discovered significant reduction in cancer recurrence in those patients taking ACEI/ARBs and diagnosed with urinary tract, colorectal, pancreatic, and prostate cancer via a significant reduction in cancer recurrence. Data indicates those with breast or hepatocellular cancer do not experience this same reduction in recurrence when taking ACEI/ARBs.

Two large case-control studies based on data from a national cancer data base in Taiwan agreed with Sipahi et al. Separate studies by Lee et al. (2012) and Chang et al. (2016) found no increased risk of breast cancer in women who used ACEI/ARBs (age >50). Similar to other studies mentioned here, authors recognized the presence of multiple variables associated with the development of breast cancer. Unfortunately, when determining outcomes, variables considered between the two studies were inconsistent.

Data from U.S. based research agreed with results from the studies in Taiwan. In 2011, the United States Food and Drug Administration (FDA) supported the position that ARBs, specifically, do not increase the risk of cancer (Townsend, 2017). Additionally, U.S. based *Up to Date* (2017), an extensive current medical data base, determined through a review of two large meta-analyses, the use of ACEI/ARBs is not associated with an increase risk of cancer. This data corroborates findings of previously mentioned studies in this review.

Benefits of Use

Several studies reviewed through this literature review determined the use of ACEI/ARBs offer a protective benefit against the development of many cancers. Yoon et al. (2011) based their research on epidemiologic studies, finding inconsistent results in terms of ACEI/ARBs and the risk of cancer. This study reviewed 3,970 articles, ultimately selecting 10 cohort studies (3,611,694 individuals) and 14 case-control studies for analysis. Overall, authors of this study determined there is no association between the use of ACEI/ARBs and overall risk of cancer (RR 0.96, 95% CI, 0.90-1.03). However, through a sensitivity analysis, they did find there may be beneficial effects with the use of either ACEI/ARBs in terms of cancer risk when the included conventional case-control studies were removed from the mix. These conflicting results indicate the need for large randomized control trials that specifically look at this possible benefit.

Napoleone et al. (2011) sought to discover if blocking the RAS system would potentially have any controlling influence on tissues in metastatic breast cancer cells. Researchers found ACEI down-regulate the expression of tissue factor in metastatic human breast carcinoma cells, thereby inhibiting cancer cell proliferation, migration, tumor growth, and metastasis. These findings, discovered in a controlled laboratory setting, indicate this beneficial effect is directly related to inhibition of the RAS by the actions of ACEI, suggesting a new potential strategy for combined methods in the treatment of cancer. Despite the presence of limitations including lack of human variables such as age, gender, genetics, and organ specific cancers, the strength of results indicate a need for further well designed research on the effects of ACEI/ARBs in cancer research.

Contradicting Sipahi et al., Lonati and Morganti (2012) found larger meta-analysis studies indicating antagonists of the RAS system may actually protect against cancer incidence

and progression. Rabel et al. (2017) upheld these findings through a large retrospective cohort study. Data collected from Kaiser Permanente, the largest non-profit, private, integrated health care delivery system in the United States included 90,078 women ≥ 55 years of age using ACEI for management of hypertension. Looking specifically at the risk of breast cancer associated with long term use of calcium channel blockers or ACEI researchers found an increased duration of ACEI use (between 1-12 years) correlated with a protective association against breast cancer.

Seeking to determine the risk associated with ACEI/ARBs and the development of solid tumor cancers, such as breast cancer, Chae et al. (2011) used a case-control study format to analyze data from a veteran affairs hospital. This small study (703 patients, mean age 59.1 years) looked at 168 patients who had used ACEI/ARB for at least six months. This group had a statistically significant lower incidence in cancer recurrence (ACE/ARB use: 15% recurrence rate; Non-use: 23%). The final conclusion of this study determined patients who used ACEI/ARBs had a significantly lower rate of breast cancer recurrence than non users. Similar results were obtained from the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) studies (Devore et al., 2015). Using data collected from 210,641 U.S. registered nurses, researchers found the use ace inhibitors imparts a decreased risk of breast cancer on women using the medication for hypertension.

Conclusion

The renin angiotensin system is a powerful mediator of multiple key elements of blood pressure regulation and homeostasis. Key players in the RAS system include angiotensin I and II (Woo & Robinson, 2016). ACEI/ARBs work to block RAS receptors, thereby effectively reducing blood pressure (Woo & Robinson, 2016). It is known that cancer cells contain angiotensin I/II receptors; these receptor sites are involved in the proliferation and angiogenesis

of cancerous tumors (Vinson, Barker, & Puddefoot, 2012). This knowledge has lead researchers to theorize ACEI/ARBs, given their mechanism of action, could have an anti-tumor effect on cancer cells. However, a firm answer as to whether or not ACEI/ARBs provide increased risk, protective benefits, or have no effect in terms of breast cancer occurrence in women, is cloudy at best given the literature reviewed here.

The literature presented in this paper contain several inconsistent confounding variables whose presence affects the variables being studied. When variables are not adjusted for appropriately in a study, confounding factors give a skewed true relationship among the variables (Pourhoseingholi, Baghestani, & Vahedi, 2012). There are multiple different variables involved in the development of both breast cancer and hypertension. These variables include, but are not limited to, ethnicity, age, menopausal status, obesity, smoking history, genetics, physical activity, and diet. Considering these confounding factors, it seems difficult to develop a true correlation between ACEI/ARBs and breast cancer occurrence.

JNC-8 guidelines recommend ACEI/ARBs as first line treatment in managing hypertension (Woo & Robinson, 2016). With 32.7% of American women diagnosed with hypertension, it is imperative that the safety, efficacy, risks, and potential benefits of these medications be thoroughly examined (CDC, 2016). The following points are key to this literature review:

- Untreated, hypertension can have devastating and long term consequences such as stroke, cardiovascular disease, and renal failure. ACEI/ARBs effectively reduce these risks (Woo & Robinson, 2016). When managing hypertension, it is imperative to prescribe medications that will control blood pressure with minimal side effects and risk to patient safety.

- Selection of medication should be based on optimizing blood pressure control with minimal, if any, effects. Researchers have theorized the angiotensin blocking effects of ACEI/ARBs may prove to be useful in the prevention or treatment of breast cancer (Napoleone et al., 2011). Further research is indicated in this area.
- The reviewed studies contain varied, inconsistent, confounding variables and research methods and more importantly, inconsistent results. There is insufficient research to prove the use of ACEI/ARBs in women with hypertension creates an increased risk for developing or preventing breast cancer. Given this lack of unequivocal evidence, it is reasonable for advanced practice providers to prescribe ACEI/ARBs, knowing the benefits of treating hypertension outweigh the low risk of breast cancer occurrence. Per the JNC 8 guidelines, ACEI/ARBs should continue to be used as first line treatment of hypertension (Woo & Robinson, 2016).

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Doi:10.1503/cmaj.101497

Appendix A

OSCE Write Up

CC: Hypertension medication-follow up

HPI: XX is a 60-year-old Caucasian female with a history significant for new diagnosis hypertension who presents to the clinic for follow-up appointment after starting Lisinopril 20 mg by mouth daily three weeks ago. Patient reports feeling overall well since starting the Lisinopril, however she does endorse a new onset of dry cough since beginning the medication. She denies signs/symptoms of upper respiratory illness. She has been monitoring her blood pressures at home since starting the medication, finding her pressures are typically running 140/80's. She did not bring her blood pressure record with her today. She has been attempting to follow a low salt, low fat diet as well as incorporating exercise into her weekly routine. She reports occasional "heartburn" symptoms relieved with 1-2 tums. Does not recall factors that increase these symptoms. Denies shortness of breath, chest pressure/pain, arm, neck, or jaw pain, nausea/vomiting, or diaphoresis associated with the heartburn.

PMH: hypertension

PSH: none

Allergies: NKDA

Medications: Multivitamin 1 tablet daily, Lisinopril 20 mg daily

Social History: 20 pack/year history, quit 10 years ago, married, retired RN

Family History: father-cardiovascular disease including "open heart surgery"; Brother-hypertension; Sister-hypertension

ROS

Constitutional: negative for fevers, chills, or sweats. Negative for fatigue.

HEENT: Negative for headache, dizziness, lightheadness, ear/eye pain/drainage, sinus congestion, epistaxis, sore throat, or dysphagia

CV: Negative for chest pain/discomfort or palpitations

Resp: Negative for shortness of breath, wheezing. Positive for cough.

GI: Negative for n/v/c/d or melena. Positive for “heartburn”

GU: Negative for dysuria, frequency, incontinence, or hematuria

Integumentary: Negative for rashes, wounds, bruising

Physical Exam

Vital Signs: 160/98, P 80, RR 20, T 98.6

Constitutional: alert and oriented. Pleasant. In no obvious distress. Well nourished. Afebrile.

HEENT: normocephalic, TM’s normal, external ear normal. EOM’s intact, no redness, drainage.

Pupils PEARRL. Nares patent bilaterally and without drainage. Oropharynx pink, moist, and without exudate. No thyromegaly noted. Neck is soft, supple with normal ROM.

CV: S1S2, regular rate and rhythm. No edema noted.

Resp: Lung sounds clear throughout all fields. Normal work of breathing.

GI: Abdomen is soft, non-tender to palpation

Integumentary: turgor normal, skin color normal, warm and dry. No bruising, rashes, wounds, or petechiae noted

Assessment

XX is a 60-year-old Caucasian female with a history significant for new diagnosis hypertension who presents to the clinic for follow-up appointment after starting Lisinopril 20 mg PO daily

three weeks ago. Patient reports feeling overall well with starting Lisinopril, however endorses new onset of dry cough since starting medication. Lung sounds clear throughout all fields, normal work of breathing, afebrile, denies shortness of breath. Likely cause of cough is related to common side effect of Lisinopril; low suspicion for infectious etiology. Per patient, blood pressures at home consistently running 140/80's- within JNC 8 guidelines for goal pressures given patient's age. Today's elevated pressures may be related to anxiety over clinic visit. Concerns for GERD given recent history of "heart burn" relieved with Tums.

Plan

Hypertension

1. Will change Lisinopril to Losartan 50 mg PO daily in the AM in hopes this will alleviate cough while maintaining normotensive status.
2. Recommend starting 81 mg Aspirin daily for heart health.
3. Labs today: CBC, Chem 8 to assess kidney function, Hgb. Baseline EKG. Baseline chest x-ray (cardiomegaly).
4. Reiterate importance of low salt diet, exercise, stress reduction. Maintain a healthy weight.
5. Return to clinic in 3 weeks for repeat Chemistries to assess renal function after starting Losartan.
6. Continue to check blood pressure at the same time each day. Bring blood pressure diary to appointment in 3 weeks. Will recheck blood pressure in clinic at that time as well.
7. Seek immediate care for persistent headaches or acute neurological deficits indicating CVA.

GERD

1. Continue TUMS per package directions for infrequent acid reflux symptoms. May use OTC Zantac for symptoms as well. Follow the package directions.
2. If GERD symptoms become persistent, will start PPI vs consistent H2 blocker.
3. May need to consider EGD.
4. Instruct patient to monitor for melena, occult blood in stools, hematemesis indicating GI bleed. Seek medical care immediately if either of these occur.
5. Instruct patient to follow a low salt, low fat, low acid diet. Avoid caffeine, spicy foods, alcohol, and smoking as these may increase GERD symptoms.
6. Prop the head of the bed up with 6 inch blocks to help keep gastric acid from entering the esophagus. Do not lay down for 30 minutes after eating.
7. Advise patient when to seek immediate medical attention indicating acute coronary syndrome: chest pain, pressure, or discomfort that may radiate to neck, jaw, or arm, shortness of breath, nausea/vomiting, sweating.

Health Maintenance

1. Mammograms yearly
2. Fasting serum glucose, cholesterol panel
3. Yearly influenza vaccination
4. Pneumonia vaccination after age 65
5. DEXA scan to monitor mineral bone density
6. Colon cancer screening

Appendix B

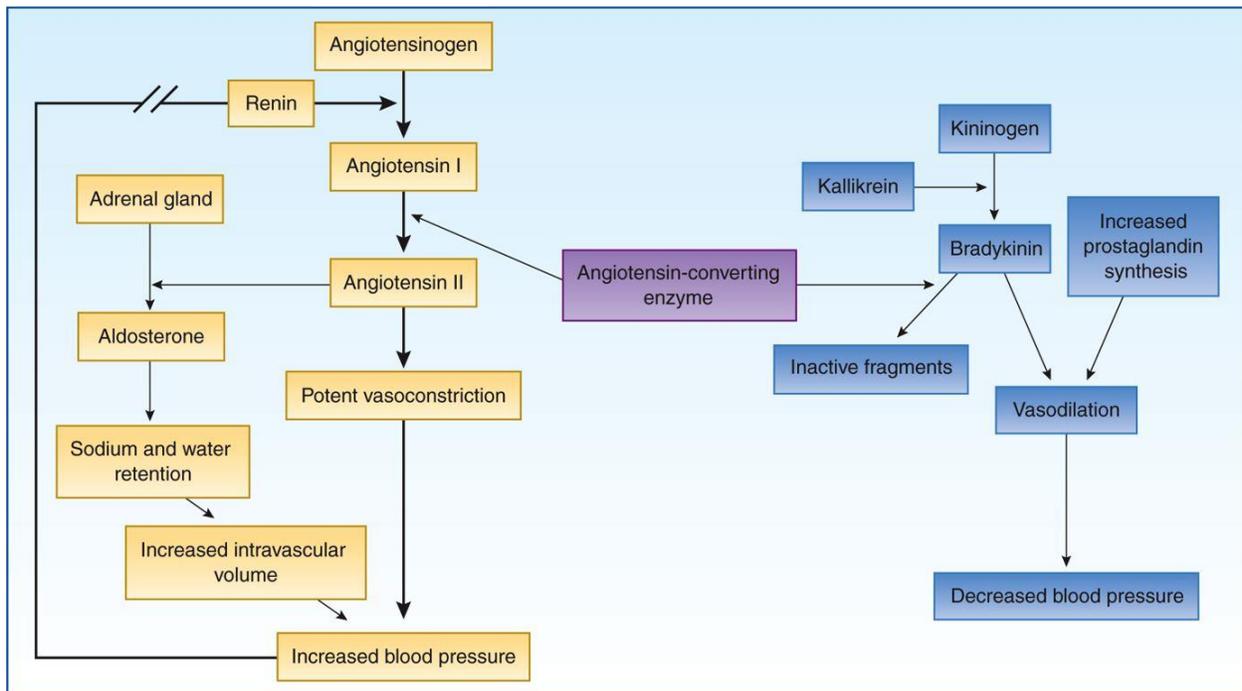


Table 1. Renin-angiotensin aldosterone system. (Woo & Robinson, 2016).