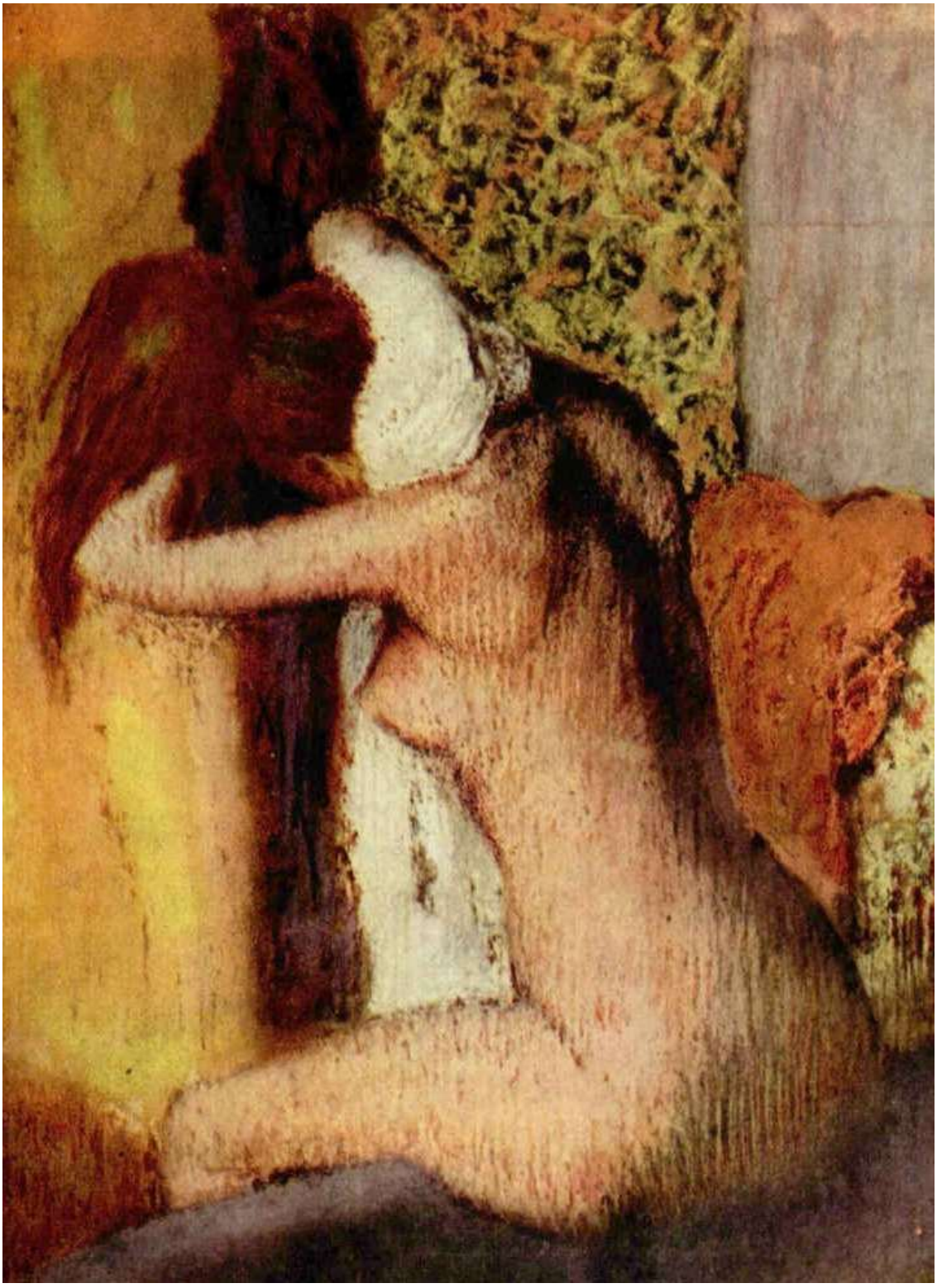
THE NORTHERN HOSPITAL

SACUBITRIL - VALSARTAN



"After the Bath, Woman Drying Her Nape", pastel on paper, 1895, Edgar Degas

Auguste de Gas had had high hopes of his son becoming a lawyer, perhaps even to join him in the family business of banking. But things would not quite go the way he had intended. Auguste was a friend of the wealthy art connoisseur Edouard Valpincon, who happened to own a masterpiece by the Neoclassical master Jean Auguste Dominique Ingres. This work was one Ingres' most famous and it was known simply as the "Bather". It must have been through his father that Edgar as a teenager had one day been at the house of Valpincon, when he caught site of the painting. From the first he was spellbound, not able to take his eyes from it. Perhaps he had never seen a nude woman before, but whatever it was that entranced him that day the image was seared into his subconscious just as a baby chick who first sees its mother when it comes into the world, and this powerful and erotic image would remain with him for the rest of his days. Many years later when Edgar had become one of the most famous and greatest Impressionists, the image of the Valpincon bather, would remerge again and again in his brilliant pastels.

In 1855 a major exhibition of Ingres' works was to be held at the Universal Exhibition of that year. Edgar's veneration of Ingres became clear for all, when upon hearing that Valpincon had refused to lend the Bather to the exhibition, Edgar with astonishing élan for a 21 year old paid a personal visit to Valpincon and in a rage berated him for his selfishness! So persuasive was Edgar, that Valpincon thought better of it and lent his masterpiece to the exhibition and so introduced it to the greater public and today the Bather hangs in the Louvre as one of its greatest treasures. So impressed with Edgar were the organizers of the Exhibition, that an introduction to the great man himself was arranged. Edgar was so nervous meeting his hero that he hesitated to mention to him that he was in fact thinking of become a painter himself, but he did manage to draw up his courage and blurt it out eventually. Ingres, amused, replied, "Well then young man, draw lines, lots of lines, never from nature, always from memory and the engravings of the masters". The meeting came to an abrupt end when Ingres, by then seventy five years old, had a fainting spell, requiring Edgar to leave.

Ingres had studied under the immortal Jacques Louis David, and so was trained in the Neoclassical school. So an exact and superb a draftsman was Ingres that he laid many of the foundations of the formal Academic style of the early to mid Nineteenth century. And yet at the same time he did have his own unique style, the classical influences of his boyhood hero Raphael and the elegant elongated forms of the Mannerists, whom he much admired whilst studying in Italy in his youth, are plain to see in his works. Just as Ingres brought his own individual signature to the Neoclassical style, so would Edgar bring his own style to the Realist painters of the mid Nineteenth century - a movement incidentally which sought to reduce the immensely strong influence of the Neoclassicists and the monopoly of "taste" then held by the Salons. Edgar, of course went on to become far more radical than anything Ingres or his generation could possibly have ever even dreamed of, and yet buried by colour warmth and movement within Edgars most brilliant Impressionist Bathers, are found the basic motifs of the Valpincon bather, the smooth lines of the back, the attention to the nape of the neck, the anonymous three quarter turned profile. But while Ingres depicts a cold, detached and academic eroticism, Degas in his bathers positively radiates warmth and intimacy. The lines of Ingres are rigid and formal, as for a classical Greek statue. The model is very much posing for the moment. The only sound or movement we glean from the Valpincon bather is a small fountain trickling at the lower left, the rest of the image is rigidly frozen in space as well as in

time. While Ingres valued line above color he did not entirely neglect the effects of colour, though muted these were. In the bather we see a subtle and clever gradation of darkness to light moving from the left to the right of the work. But in Degas's bathers, color is ablaze and harmoniously blended with line to give a more living image. One is within the boudoir itself with the model, though she may not be aware of the fact herself!

To best understand the brilliant Impressionist, Edgar Degas we must understand the profound primal influences at play in his works. And so it is with our patients in Heart Failure. To best understand this ubiquitous disease, we must understand its primal underlying influences. For many years we thought we had the complete picture; heart failure resulted from an excessive and detrimental activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. And yet this was not the whole story. It is now recognized that a third critically important influence is at play, the natriuretic peptide hormones, that seek to redress the detrimental influences of the other two. In the novel agent sacubitril - valsartan a new dawn arises in the understanding and treatment of heart failure with reduced ejection fraction.

"The Bather (or the Valpincon Bather)",
oil on canvas, 1808,
Jean Auguste Dominique Ingres
Musee du Louvre.

Below: formal harmonious lines of composition were an important part of "Academic" Art.

SACUBITRIL - VALSARTAN

Introduction

Sacubitril-valsartan (trade name in Australia "**Entresto**") is a novel combination drug used in the treatment of **NYHA class II - IV**, **chronic heart failure** with **reduced ejection fraction**.

It consists of the **neprilysin inhibitor prodrug, sacubitril** and the **angiotensin receptor blocker (ARB), valsartan**

It aims to *enhance* the **natriuretic peptide system** and at the same time to *inhibit* the **renin - angiotensin - aldosterone system**

Sacubitril (*pronounced sacube - itril*) is the first **neprilysin inhibitor** to be introduced into clinical practice

Sacubitril - valsartan is the first drug combination developed for clinical used in the class of **angiotensin receptor - neprilysin inhibitors** (**ARNIs**).

The combination is given in **place of** an **ACE inhibitor** or other **angiotensin receptor antagonist**, in addition to other drugs of different classes for heart failure.

The principal adverse effects of the combination include:

- **Hypotension (sacubitril and valsartan)**
- **Angioedema (sacubitril)**
- **Hyperkalemia (valsartan)**

See also separate documents on:

- **Valsartan**
- **Angioedema**

History

The substance **LBQ657 -** (**sacubitrilat**) was the first developed **neprilysin inhibitor** for clinical use.

During development **LCZ696** was the term applied to the combination agent **sacubitril-valsartan**

In 2015 the US Food and Drug Administration (FDA) approved the combination agent, sacubitril - valsartan for clinical use.

It was approved for clinical use in Australia in 2017.

Chemistry

Neprilysin is an endopeptidase.

LCZ696 is a molecule that **combines valsartan** and **sacubitril** (the neprilysin inhibitor) into a **single** substance.

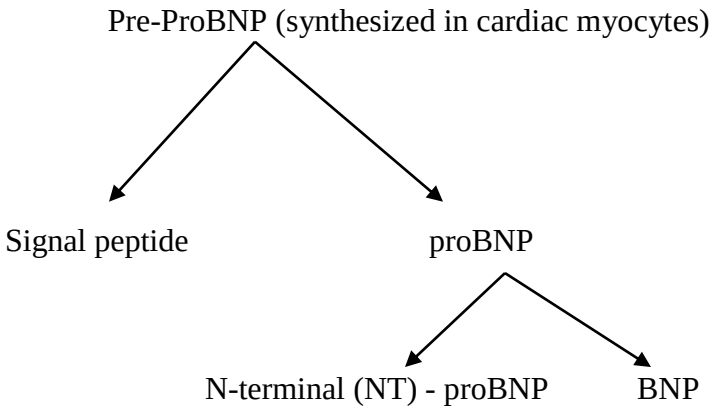
Physiology

B-type natriuretic peptide (**BNP**) is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to **excessive stretching of cardiac myocytes.**

BNP is one of three known naturally occurring natriuretic peptides. These include:

- B- type natriuretic peptide (BNP) (from ventricles)
- A- type natriuretic peptide (ANP) (from atria)
- C-type natriuretic peptide (CNP) (from vascular endometrium)

BNP is released from the cardiac ventricles, especially the left, in response to increases in end diastolic pressure or volume loading of the ventricle.



Removal of the signal peptide from the N-terminus of preproBNP results in the proBNP molecule

Then proBNP is converted by proprotein convertase into two peptides, BNP and the N-terminal part of the proBNP i.e (NT) proBNP.

BNP is the biologically active molecule.

Natriuretic peptides exert their effects by activating membrane bound **guanylyl cyclase coupled receptors**, resulting in increased concentrations of the second messenger cyclic

guanosine monophosphate (cGMP), thereby promoting their various physiological effects.

Neprilysin is an endopeptidase that **degrades** vasoactive substances such as the **natriuretic peptides**.

The normal physiological actions mediated via specific receptors for each of the three types. include:

1. Vasodilation of:
    - Arteries
    - Veins
2. Natriuresis
3. Diuresis (increases GFR)
4. Suppression of neurohumeral responses:
    - Reduction of sympathetic outflow
    - Suppression of renin
5. Direct myocardial protective effects:
    - Inhibits cardiac myocyte **hypertrophy**
    - Attenuates norepinephrine-induced proliferation of cardiac fibroblasts (so **reduces fibrosis**)

Pathophysiology

Heart Failure is a syndrome characterized by the activation of 3 neurohumeral responses:

1. Sympathetic nervous system (SNS)
2. Renin - Angiotensin - Aldosterone system (RAAS)
3. The natriuretic peptide system (NPS).

Excessive activation of the **SNS** and the **RASS** can lead to **detrimental** results in heart failure.

Pharmacological interventions have therefore been developed to counteract the neuroendocrine overregulation of:

- The SNS (with **β-blockers**).

- The RAAS (with **ACE inhibitors, ARBs** and **mineralcorticoid antagonists** or **MRAs**)

It is now known that the natriuretic peptide system *counter regulates* the *detrimental* effects of the upregulation of the SNS and the RAAS

Recently a novel class of **neprilysin inhibitors** have been developed to enhance the NP system - the **angiotensin receptor neprilysin inhibitors** or **ARNIs**.

The first of this new class is **sacubitril - valsartan**

Sustained activation of the renin angiotensin aldosterone system results in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II dependent aldosterone release.

Classification

Sacubitril is the first drug developed for clinical used in the class of **angiotensin receptor - neprilysin inhibitors** (or **ARNIs**).

Preparations

Sacubitril - valsartan as:

Tablets in fixed dose combination:

- Sacubitril 24 mg + valsartan 26 mg
- Sacubitril 49 mg + valsartan 51 mg
- Sacubitril 97 mg + valsartan 103 mg

Note that **26 mg valsartan** in these fixed-dose combinations is equivalent to **40 mg valsartan** in *other* products.

Mechanism of Action

The combination is designed to simultaneously inhibit **neprilysin** (**with sacubitril**) and the **renin–angiotensin system** (**with valsartan**).

Sacubitril:

Neprilysin is an endopeptidase that **degrades** vasoactive substances such as :

1. **Natriuretic peptides**:
    - B- type natriuretic peptide (BNP)
    - A- type natriuretic peptide (ANP)
    - C-type natriuretic peptide (CNP).
2. Bradykinin
3. Adrenomedullin

By ***inhibiting*** **neprilysin**, sacubitril **increases** the *concentration of these peptides* which in turn promotes useful effects in chronic heart failure including:

- Vasodilation
- Increased glomerular filtration rate:
    - ♥ Diuresis
    - ♥ Natriuresis
- Anti-fibrotic effects in the heart
- Anti-hypertrophic effects in the heart

These beneficial effects, however may come at the cost of 2 principal *deleterious* effects:

- Hypotension
- Angioedema (due to **increased levels** of **bradykinin** - note that valsartan does *not* increased bradykinin levels).

Valsartan:

Valsartan is an angiotensin II type 1 (AT1) receptor blocker.

They therefore ultimately **reduce** angiotensin II induced effects which include:

- Vasoconstriction
- Aldosterone release (hence sodium reabsorption, hence water reabsorption).

This brings about the following beneficial effects in chronic heart failure:

- Vasodilation
- Reduced aldosterone levels (and hence sodium (and hence water) excretion)

See also Appendix 2

Pharmacodynamics

In the PARADIGM-HF trial **sacubitril with valsartan** was superior to enalapril alone in reducing combined endpoint of **cardiovascular death** or **first hospitalisation** for heart failure by 20 %

Pharmacokinetics

Absorption:

Sacubitril:

- Sacubitril - valsartan is administered orally.

  Following oral administration, the salt complex dissociates into sacubitril and valsartan.

  Sacubitril is a prodrug that is then metabolized to the active agent **sacubitrilat**

  Sacubitril → sacubitrilat

Valsartan:

- Valsartan is administered orally.
- Peak plasma concentrations are reached 2 - 4 hours after dosing.
- The amount absorbed can vary widely, but the mean absolute bioavailability is 23%

Distribution

Sacubitril:

Sacubitrilat crosses the blood brain barrier to only a very limited extent, (0.28 %).

- It is unknown if sacubitril crosses the human placenta.
- It is unknown if sacubitril is excreted into human breast milk

Valsartan:

- Valsartan is highly bound to serum protein (94-97%), mainly serum albumin.
- Steady-state volume of distribution is low (about 17 L) indicating that valsartan does not distribute into tissues extensively.

- It is unknown if valsartan crosses the human placenta.
- It is unknown if valsartan is excreted into human breast milk

Metabolism and excretion:

Sacubitril:

- Sacubitril → sacubitrilat via esterases
- Sacubitrilat is primarily excreted in the urine.
- The elimination half-life of sacubitril, is around 1.4 hours [4]
- The elimination half-life of sacubitrilat is around 11.5 hours [4]

Valsartan:

- Valsartan does not undergo extensive biotransformation.

  Only approximately 25% of absorbed drug is metabolised to an inactive metabolite.
- The elimination half -life of valsartan is around 10 hours.

Indications

Sacubitril - valsartan is indicated as standard treatment for adult patients with:

- **Chronic heart failure** of **NYHA class II - IV** with **reduced ejection fraction**.

The combination is given in *place of* an **ACE inhibitor** or other **angiotensin receptor antagonist**, in addition to other drug classes for heart failure.

Evidence is insufficient to recommend sacubitril with valsartan as first-line treatment for heart failure at present. [1]

Currently, its exact place in the treatment of heart failure is **unclear**; possibly it may **replace the ACE inhibitor (or sartan)** in people who are still symptomatic on an ACE inhibitor or sartan, beta-blocker and aldosterone antagonist. [1]

Contra-indications/precautions

These include:

1. Known allergy to sacubitril or valsartan.
2. Hypekalemia (correct before commencing therapy)

3. Drug interactions:

- Drugs which can raise potassium levels:
  - ♥ Avoid combining with drugs which can increase potassium levels or at least monitor potassium concentrations closely.
- ACE inhibitors (contraindicated):
  - ♥ To minimise the risk of angioedema, *concomitant* treatment with an ACE inhibitor is contraindicated
  - ♥ A washout period of 36 hours is recommended before sacubitril - valsartan is initiated in patients switching from an ACE inhibitor (to reduce likelihood of angioedema).
- Other ARBs (sartans) (contraindicated)

4. Hypotension (caution if BP < 100 mmHg systolic).

- Reduce the starting doses in patients with systolic of BPs 100 - 110 mmHg or who have other risk factors for hypotension and monitor carefully.

5. History of angioedema:

- As sacubitril with valsartan treatment increases the risk of angioedema compared to sartans or ACE inhibitors, it is contraindicated with a history of **angioedema due to ACE inhibitors or sartans, or hereditary or idiopathic angioedema**.

  Note that sartans do *not* tend to cause angioedema (but ACEI do). It is the **sacubitri**l which is most likely to cause angioedema (by raising bradykinin levels).

6. Renal:

- Reduce starting dose when the eGFR is <60 mL/minute/1.73 m^2.

  Use cautiously if the eGFR <30 mL/minute/1.73 m^2 (this group was excluded from the pivotal trial); adverse effects are more severe than in mild or moderate impairment.

  Renal impairment may worsen, especially in people with hypovolaemia, or if used with NSAIDs (including selective COX-2 inhibitors).

  It also increases the risk of hyperkalaemia with sacubitril with valsartan.

  The risk of renal failure in bilateral renal artery stenosis is increased.

7. Hepatic:

- Contraindicated in severe (Child-Pugh class C) hepatic impairment (no data).

  Use cautiously and reduce starting dose in moderate hepatic impairment (Child-Pugh class B) or if AST/ALT > twice ULN.

8. Elderly:

- Symptomatic hypotension is more likely in people >75 years; consider using a lower starting dose.

9. Women should use effective contraception during and for 1 week after stopping treatment.

10. Pregnancy & breast feeding (contraindicated, see below).

Neprilysin and amyloid:

- Neprilysin is involved in the clearance of amyloid-beta. Increased concentrations have been found in the cerebrospinal fluid of healthy adults taking sacubitril/valsartan. The clinical relevance of this is currently unknown. [4]

  The effect of sacubitril on cognitive function and amyloid plaque deposition in the brain needs to be elucidated.

Pregnancy

Sacubitril

There is no human data for sacubitril effects in pregnancy, however teratogenic effects in animal studies have been observed, therefore sacubitril should not be used in pregnancy.

Valsartan

Valsartan is contraindicated in pregnancy.

It is classified as a category D class drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Limited information is available describing the use of valsartan during pregnancy.

Treatment with angiotensin II receptor antagonists in the first trimester of pregnancy presents a lower risk for adverse fetal outcomes compared to later trimester exposure.

Maternal treatment with angiotensin II receptor antagonist during the second and third trimester have been associated with renal failure, pulmonary hypoplasia, skull hypoplasia, limb contractures, oligohydramnios and fetal or neonatal death.

When pregnancy is suspected, treatment with angiotensin II receptor antagonist should be discontinued immediately and changing to an alternative antihypertensive, such as methyldopa or labetalol is recommended to minimise the risk of fetopathy.

A careful prenatal examination, including high-resolution ultrasound at the 16th to 20th week of gestation and monitoring of amniotic fluid volume, should be offered to women who have taken angiotensin II receptor antagonist during the first trimester.

Breast feeding

Sacubitril

These is no data available regarding sacubitril in breast feeding, therefore *avoid* in breastfeeding.

Valsartan

Avoid, insufficient data

Reports describing the use of valsartan during breastfeeding have not been located, and the effects on the breastfed infant are unknown.

Therefore, consider an alternative medicine where possible.

If used, shorter acting angiotensin converting enzyme (ACE) inhibitors such as captopril or enalapril are preferred and considered safe to use during breastfeeding.

Adverse Effects

These include:

1. Hypotension:

    - Hypotension is more common with sacubitril/ valsartan compared to enalapril alone.

      Hypotension is a valsartan *and* sacubitril effect

      The risk of it occurring is higher in: [4]

      ♥ Older age (≥ 75 years)

- ♥ Those with low baseline systolic blood pressure
- ♥ Patients with renal disease
- ♥ Patients on high-dose diuretics

2. Bradykinin effects:
   - Sacubitril can elevate bradykinin levels leading to
     - ♥ Cough
     - ♥ **Angioedema**
     - ♥ Hypotension
3. Hyperkalemia:
   - Hyperkalemia is a valsartan effect
4. Renal impairment

Dosing [1]

Dosing is expressed as sacubitril / valsartan.

A washout period of at least **36 hours** is recommended before sacubitril - valsartan is initiated in patients switching from an ACE inhibitor (to reduce likelihood of angioedema or hypotension) or a sartan, (to reduce likelihood hypotension)

The recommended starting dose of sacubitril - valsartan is **49 mg / 51 mg twice daily**

A lower starting dose using the **24 mg / 26 mg** preparation should be considered in patients: [4]

- Not currently taking an ACE inhibitor or angiotensin receptor antagonist,
- Who have risk factors for hypotension such as:
- > 75 years
- With systolic blood pressure < 100 mmHg
- With severe renal impairment
- With moderate hepatic impairment

If tolerated doses can be increased to **49/51** or **97/103** depending on the starting dose if required after 2 - 4 weeks.

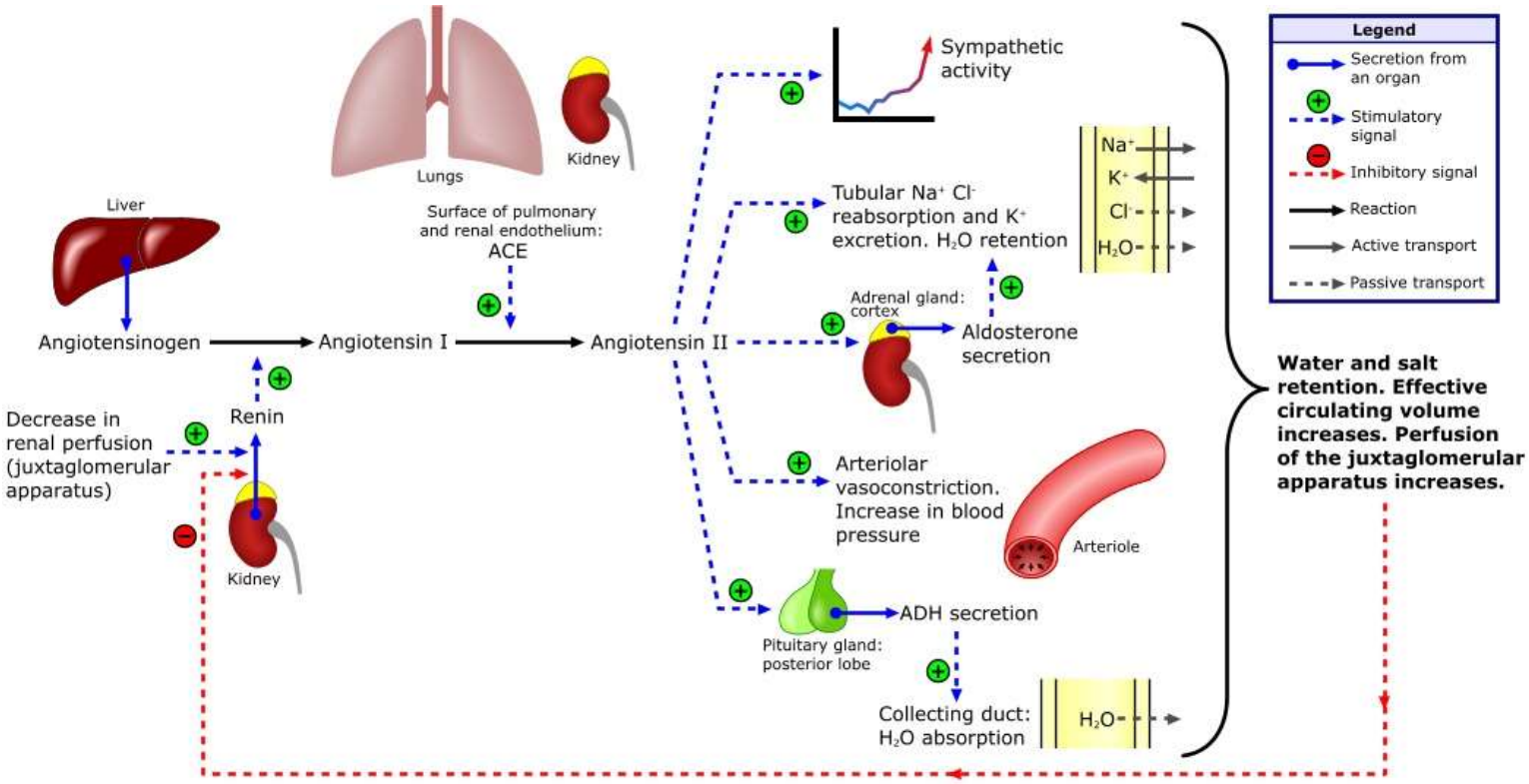
Appendix 1

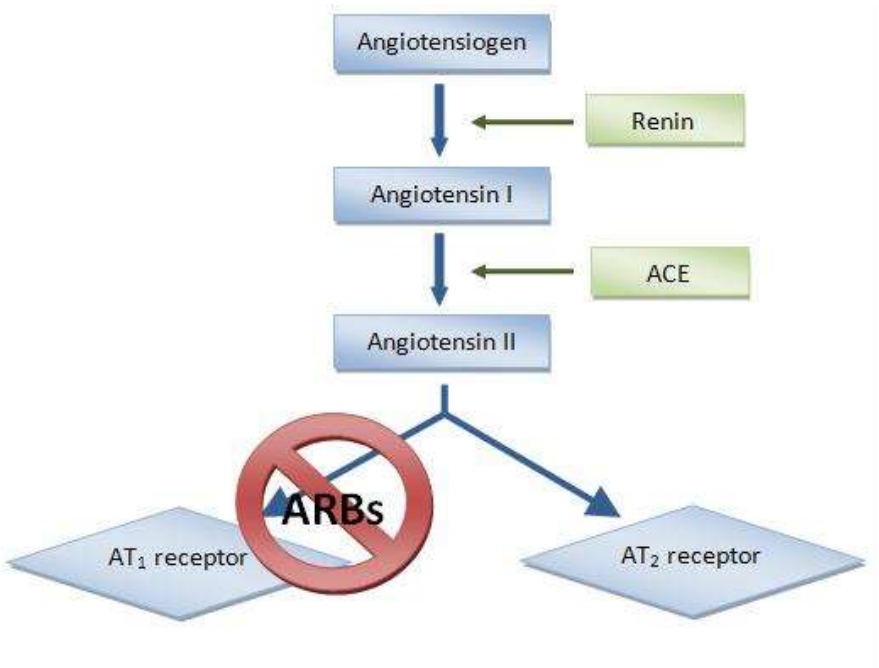
The New York Heart Association Heart Failure Classification:

CLASS	Features
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

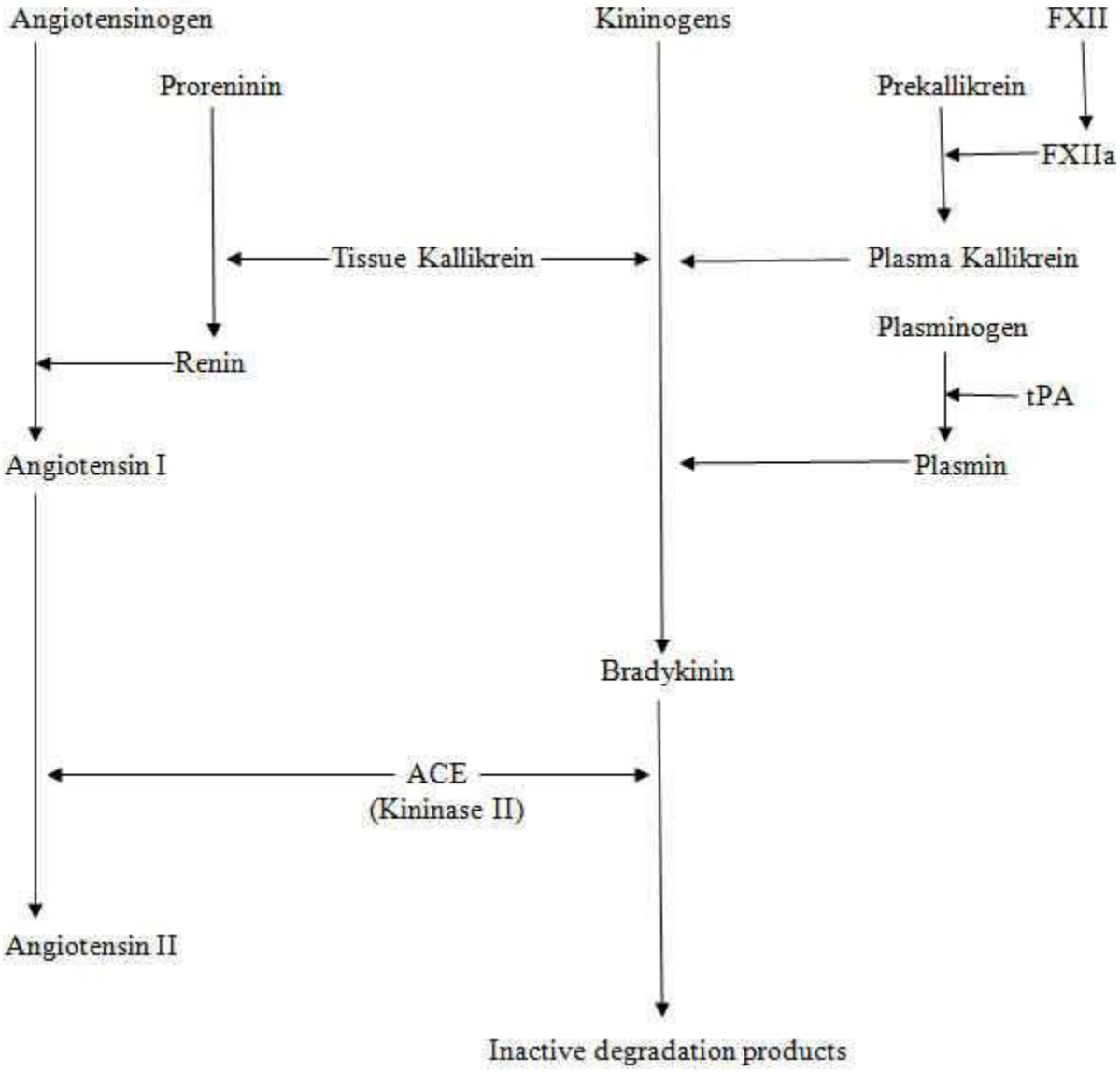
Appendix 2

The Renin - Angiotensin - Aldosterone System:





Appendix 3



Biochemical pathways, demonstrating some of the relationships between tissue plasminogen, bradykinin and ACE, in the pathogenesis of angioedema.

References

1. Sacubitril-valsartan in Australian Medicines Handbook Website Accessed, June 2017.

2. Sacubitril-valsartan in MIMs Website, 1 March 2016.

3. Valsartan in RWH Pregnancy & Breastfeeding Guidelines; 16 SSeptember 2016.

4 Sacubitril/valsartan. Aust Prescr 2016; 39: 226 - 7

- dx.doi.org/10.18773/austprescr.2016.080

5. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.

- dx.doi.org/10.1056/NEJMoa1409077

6. Massimo Volpe et al. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. Clinical Science (2016) 130, 57 - 77

- doi: 10.1042/CS20150469

Dr J. Hayes
9 July 2017.