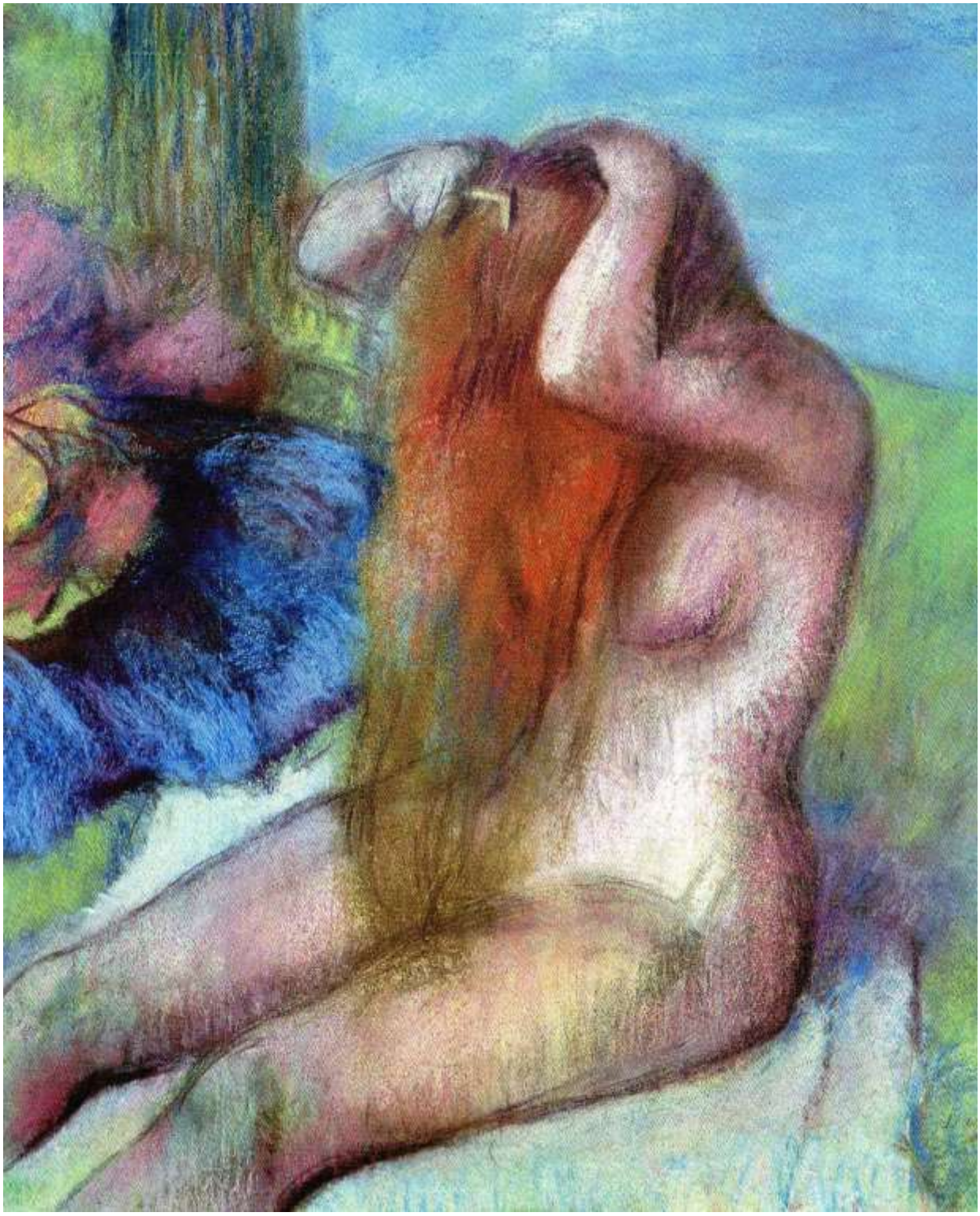
THE NORTHERN HOSPITAL

TELMISARTAN



"Woman Combing Her Hair", pastel on paper, c. 1895, Edgar Degas.

"Art is not what you see, but what you make others see…..

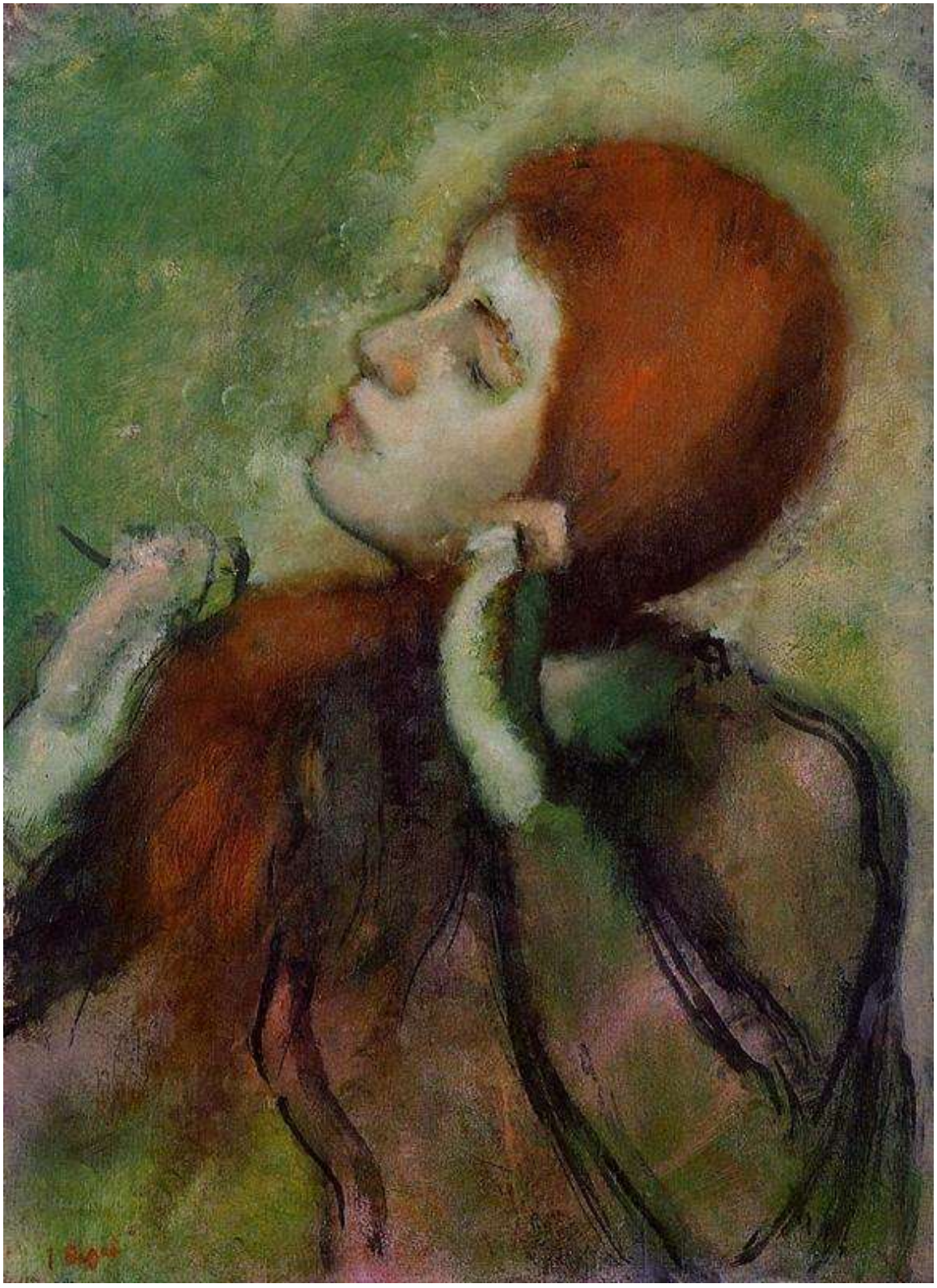
It is very good to copy what one sees; it is much better to draw what you can't see any more but is in your memory. It is a transformation in which imagination and memory work together. You only reproduce what struck you, that is to say the necessary....

Edgar Degas

Edgar Degas' pastels of bathers share many similar features, over and over we see glorious use of light, colour and line that give an impression of movement in a private and perfectly natural moment. The bathers go about their ablutions, unaware they are being observed. He sketched countless thousands of works of his models from life, however these rarely resulted in the final work. Rather they merely served as blueprints, stored away for future use, sometimes days later, sometimes many years later. He would take his blueprint, then mold it in his mind to produce endless variations on a similar theme. "It is very good to copy what one sees; it is much better to draw what you can't see any more but is in your memory", Edgar once quipped. He worked his memory within his imagination and moulded it into something brilliant and new, "a transformation in which imagination and memory work together". In this way he produced, not reality but only what had struck him about the moment, "You only reproduce what struck you, that is to say the necessary", he explained. In this way he took reality but made it into something more, something that he wanted people to see, "Art is not what you see, but what you make others see….." From "so simple a beginning", Edgar within his imagination produced for posterity "endless forms most beautiful and most wonderful".

One bather model in particular seems to have struck Edgar most particularly. She is a striking redhead with long flaming red hair, perhaps a dancer at the Paris Opera. We never see her face, as most with most of Degas' bathers. It is not the person that is important, but rather the fleeting moment, the feeling, the emotion, the warmth, the Impression. On the very rare occasion we do see a face, the image is bland, almost to the point of generic. We see one striking example of woman combing her hair, circa 1894. Her eyes are closed, she is in her own world, we do not know her thoughts, we do not know who she is, but Edgar's message to the viewer is the same; the moment, movement, light colour, glowing warmth.

Big Pharma produces a winner! Suddenly the Impression is overwhelming, the latest wonder drug has arrived, and billions are made! In short order an endless flurry of "me too" drugs follow in its brilliant wake. Like Degas' redheaded Bather, Losartan came like a comet onto the scene....then followed the rest, but in essence all simply variations of the original blueprint, the essential message being the same!



“Woman Combing Her Hair”, pastel on paper, c. 1894 Edgar Degas.

TELMISARTAN

Introduction

Telmisartan is an **angiotensin receptor blocker (ARB)**

The ARBs are also known as :

- **Angiotensin II antagonists**
- **Sartans**

Current expert opinion does **not** attribute angioedema to Angiotensin II receptor blockers, indeed on theoretical grounds alone, it would *not* be expected to produce this side effect.

The sartans are primarily indicated in situations where ACE inhibitors are not tolerated due to adverse reactions.

See also separate document on ACE inhibitor Overdose (in Toxicology folder) - toxic overdose effects are similar to the ACE inhibitors

History

Saralasin was developed in the early 1970s. It was an analogue of angiotensin II, but had low oral activity, short duration of action and was a partial agonist.

Eprosartan was developed in 1992.

Losartan was the first angiotensin II receptor blocker to be developed for **clinical use** in 1986.

From losartan the following were then developed:

- Valsartan, Candesartan, and Irbesartan were introduced in 1990.
- **Telmisartan** was introduced in 1991
- Olmesartan was introduced in 1995.

Classification

ACE Inhibitors (ACEI) include:

1. Captopril
2. Enalapril
3. Fosinopril

4. Lisinopril
5. Perindopril
    - Perindopril (arginine)
    - Perindopril (erbumine)
6. Quinapril
7. Ramipril
8. Trandolapril

Angiotensin II receptor blocking (ARB - also known as "sartan") agents include:

1. Candesartan
2. Eprosartan
3. Irbesartan
4. Losartan
5. Olmesartan
6. **Telmisartan**
7. Valsartan

Preparation

Telmisartan as:

Tablets:

- 40 mg, 80 mg (including with combination preparations).

Fixed-dose combinations:

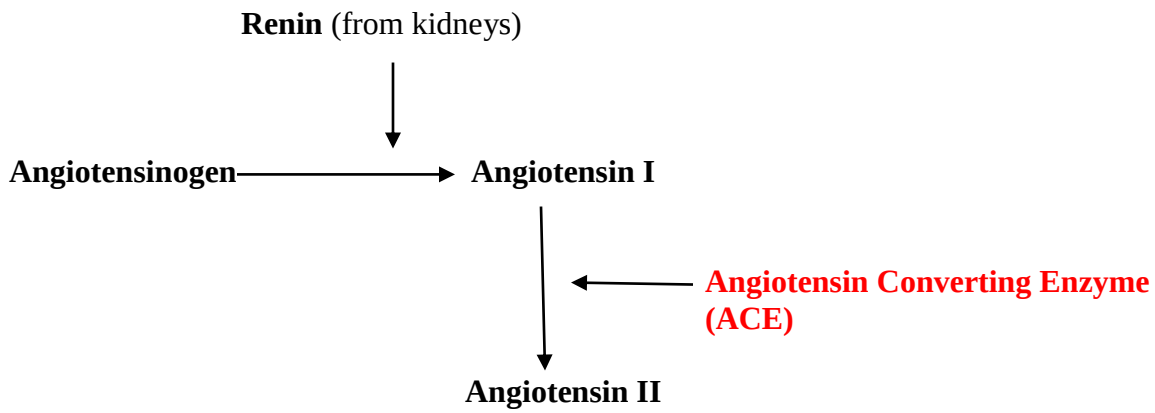
Telmisartan with **hydrochlorothiazide**:

- Telmisartan 40 mg + hydrochlorothiazide 12.5 mg
- Telmisartan 80 mg + hydrochlorothiazide 12.5 mg
- Telmisartan 80 mg + hydrochlorothiazide 25 mg

Telmisartan with **amlodipine.**

- Telmisartan 40 mg + amlodipine 5 mg
- Telmisartan 40 mg + amlodipine 10 mg
- Telmisartan 80 mg + amlodipine 5 mg
- Telmisartan 80 mg + amlodipine 10 mg

Physiology



The renin-angiotensin-aldosterone system (see also Appendix 2 below)

The actions of angiotensin II are mediated by angiotensin receptors:

1. AT_1
    - Vasopressor effects
    - Regulates aldosterone secretion
2. AT_2.
    - Plays a role in fetal stimulation of cell growth
    - This receptor has **not** been shown to be associated with cardiovascular homeostatic physiology.

Mechanism of Action

The ARBs competitively block the binding of angiotensin II to **type 1** angiotensin (AT1) receptors.

They therefore ultimately reduce angiotensin II induced effects including:

1. Vasoconstriction

2. Sodium reabsorption

3. Aldosterone release.

Note that the **sartans** do **not** inhibit angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and **no** potentiation of bradykinin or substance P, angiotensin II receptor antagonists are **unlikely** to be associated with cough or angioedema. [3]

Pharmacodynamics

1. Lowering of blood pressure:

    - In hypertension, candesartan causes a dose dependent, long lasting reduction in arterial blood pressure. The antihypertensive action is due to decreased systemic peripheral resistance, while heart rate, stroke volume and cardiac output are not affected.

    - After the first dose of telmisartan, the onset of antihypertensive action occurs gradually within 3 hours.

    - The maximal reduction in blood pressure is generally attained 4 - 8 weeks after the start of treatment.

2. High cardiovascular risk, heart failure, post MI: [2]

    - Sartans have **not** been shown to be superior to **ACE inhibitors** for chronic heart failure, vascular disease, high-risk diabetes or left ventricular failure/dysfunction post MI.

      However, they do improve prognosis and are an alternative for patients unable to tolerate ACE inhibitors. Candesartan and valsartan are marketed for chronic systolic heart failure and valsartan for left ventricular failure/dysfunction after MI.

3. Hyperkalemia, (via reduction on aldosterone levels) i.e a **potassium sparing** effect.

Pharmacokinetics

Absorption:

- Telmisartan is administered orally.

- Absolute bioavailability of telmisartan is dose dependent. The mean absolute bioavailability of 40 mg telmisartan is 40 %, whereas the mean absolute bioavailability of a 160 mg dose is about 60%.

Distribution:

- Telmisartan is highly bound to plasma protein (> 99.5%).
- The mean steady-state apparent volume of distribution (Vdss) is approximately 6.6 L/kg.
- It is unknown if human placental transfer occurs.
- It is unknown if telmisartan is excreted into human breast milk.

Metabolism and excretion:

- Telmisartan undergoes substantial first-pass metabolism by conjugation to the acylglucuronide. No pharmacological activity has been shown for this conjugate.
- Telmisartan is **not** metabolised by the cytochrome P450 system.
- Telmisartan (not metabolized by first pass metabolism) is excreted in the GIT, as unchanged compound.

Indications

1. Hypertension:
    - Includes fixed-dose combination preparations with hydrochlorothiazide or amlodipine.
2. Chronic systolic heart failure:

    As part of standard treatment (e.g. with beta-blockers, diuretics) in:

    - Patients unable to tolerate ACE inhibitors
    - With ACE inhibitor (in refractory cases on specialist advice only)
3. High cardiovascular risk, heart failure, post MI: [2]
    - Sartans have **not** been shown to be superior to **ACE inhibitors** for chronic heart failure, vascular disease, high-risk diabetes or left ventricular failure/dysfunction post MI.

      However, they do improve prognosis and are an alternative for patients unable to tolerate ACE inhibitors. Candesartan and valsartan are marketed

for chronic systolic heart failure and valsartan for left ventricular failure/dysfunction after MI.

Note on concomitant treatment of ACE inhibitors with sartans:

Treatment with an **ACE inhibitor *and* a sartan**: [2]

- In trials the combination worsened renal function and increased the risk of symptomatic hypotension and hyperkalaemia
- The combination did not provide additional benefit in patients at high risk of vascular disease nor improve survival in patients with left ventricular failure/dysfunction after MI
- Aldosterone antagonists are preferred to sartans in patients with heart failure who remain symptomatic despite optimal treatment with an ACE inhibitor and a beta-blocker.

Despite conflicting trial results, it may still be an option for **selected** patients with chronic heart failure or non-responsive blood pressure, **seek specialist advice.**

Contra-indications/precautions

These include:

1. Hyperkalaemia (contraindicated):
    - Including concomitant treatment with drugs that can increase potassium concentration, avoid these combinations or monitor potassium concentration closely.
    - Renal impairment increases risk of hyperkalaemia and may affect the excretion of some sartans; use lower initial doses and monitor potassium concentration.
2. Bilateral renal artery stenosis (contraindicated).
3. Renal impairment:
    - Renal impairment increases the risk of hyperkalaemia and may affect the excretion of some sartans; use lower initial doses and monitor potassium concentration.
    - Lower doses may be required if the C r Cl is <30 mL/minute.
4. Hypotension:
    - This, like ACE inhibitors, can be most pronounced with the **first dose.**

5. Elderly:

- May be more predisposed to first-dose hypotension, hyperkalaemia and renovascular disease than younger patients.

  Start treatment with lower doses; monitor renal function closely.

6. Pregnancy - (contraindicated - see below).

7. Known hypersensitivity (rare)

Pregnancy:

Telmisartan 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 telmisartan 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:

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

Therefore, consider an alternative medicine where possible.

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

Adverse Effects

The principle adverse reactions include:

1. Hyperkalemia

2. Renal impairment:

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

   Serum creatinine may increase after starting treatment or increasing the dose (usually stabilizes within the first 2 months):

   - If increase is < 30 % or glomerular filtration rate (GFR) reduction is < 25%, there is no need to adjust dose

   - If increase is > 30% (or GFR reduction is > 25%), investigate other causes and if necessary, reduce dose or stop sartan and consider specialist referral.

3. Sartans increase risk of renal failure in bilateral renal artery stenosis.

4. Teratogenic effects in pregnancy.

Dosing

Usual dosing is:

- 40 - 80 mg daily (including with fixed dose combination formulations).

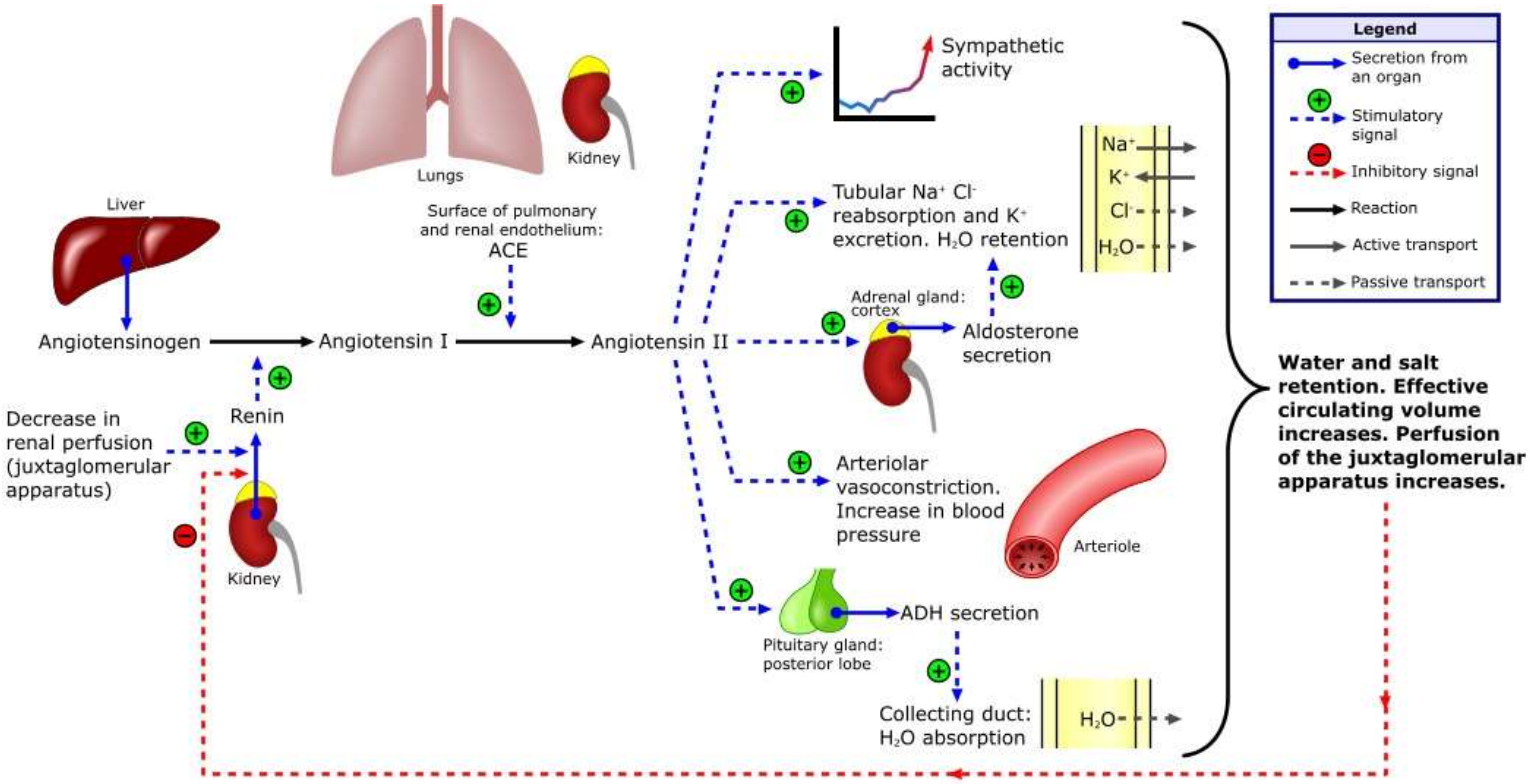
Dosage in heart failure:

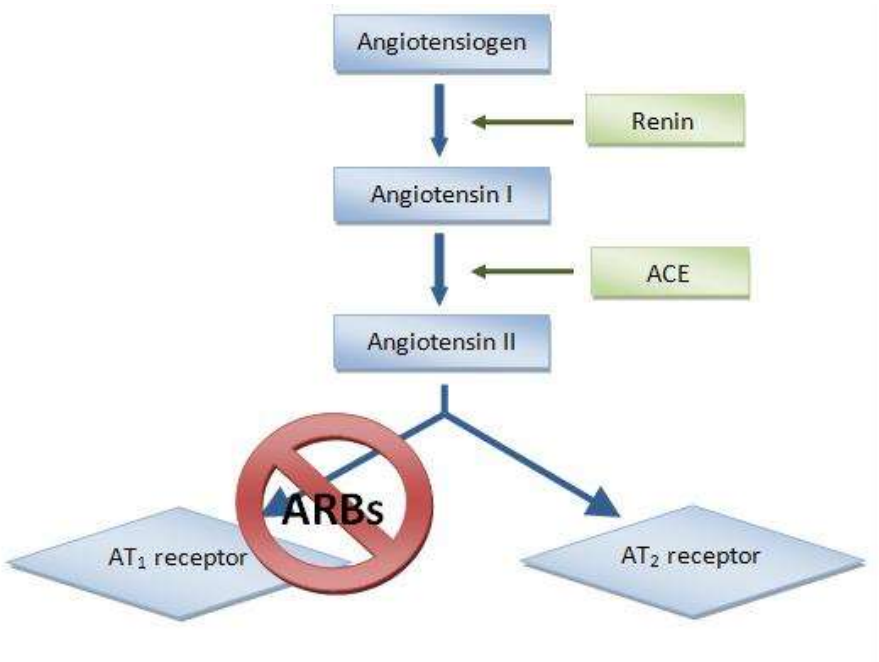
- Begin with a low dose (risk of hypotension, particularly if the patient is elderly or taking a diuretic), then gradually titrate upwards at short intervals (e.g. every 2 - 4 weeks) to the highest tolerable maintenance dose.

  A more rapid dose escalation may be possible in closely monitored situations.

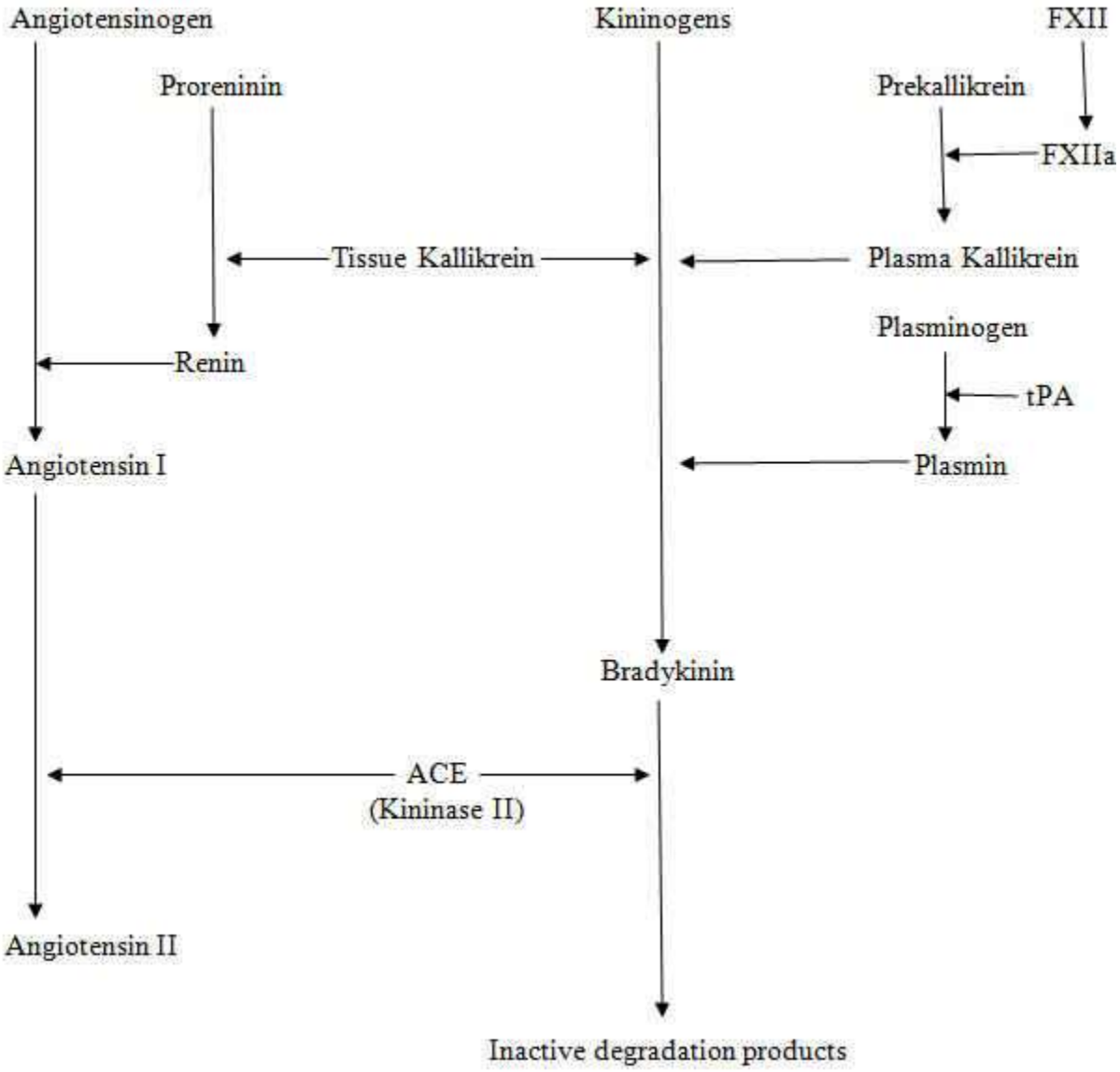
Appendix 1

The Renin - Angiotensin - Aldosterone System:





Appendix 2



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

References

1. eTG - March 2017

2. Telmisartan in Australian Medicines Handbook Website Accessed December 2015.

3. Telmisartan in MIMs Website, 1 Sep 2015.

4. Telmisartan in RWH Pregnancy & Breastfeeding Guidelines; 16 September 2016

Dr J. Hayes.
Reviewed July 2017.