

RAMIPRIL



*“Lodovico Manin”, oil on canvas, c. 1790, Bernardino Castelli, Museo Correr, Venice.*

*Judenberg, 20 germinal, year V.*

*All the mainland of the Most Serene Republic, is in arms. On every tide, the rallying cry of the peasants whom you have armed is "Death to the French!" they have already claimed as their victims several hundred French soldiers of the Army of Italy. In vain do you try to shuffle of responsibility for the militia that you have brought into being. Do you think that just because I am in the heart of Germany I am powerless to ensure respect for the foremost people of the universe? Do you expect the French legions of Italy to tolerate the massacres that you have stirred up? The blood of my brothers - in - arms shall be avenged, and there is not one French battalion that, if charged with such a duty, would not feel the doubling of its courage, the trebling of its powers.*

*The Venetian Senate has answered the generosity we have always shown with the blackest perfidy. I send you my principal aide - de - camp as bearer of the letter. Is it to be war or peace? If you do not take immediate measures to disperse these militias, if you do not arrest and deliver up to me those responsible for the recent murders, war is declared. The Turk is not at your gates. No enemy threatens you. You have deliberately fabricated pretexts in order to pretend to justify a rally of the people against my army. It shall be dissolved within 24 hours. We are no longer in the days of Charles VIII. If, against the clearly stated wishes of the French Government, you impel me to wage war, do not think that the French soldiers will follow the example of your own militias, ravaging the countryside of the innocent and unfortunate inhabitants of the terra firma. I shall protect those people, and the day will come when they will bless the crimes that obliged the Army of France to deliver them from your tyranny.*

**BONAPARTE**

*Upon reading out the letter to Doge Lodovico Manin and his full Collegio, Napoleon's aide - de - camp, General Jean-Andoche Junot, flung it down on the table in front of him, turned on his heel, and strode briskly out of the room. What followed was stunned and unbelieving silence. Never had the Doge of Venice in its thousand years of existence been spoken to in such a way. For over seventy years the Most Serene Republic had been in terminal decay. The oligarchy that now ruled Venice from an ivory tower, had become used to riches and luxury, and by a policy of unrelenting neutrality they had hoped to remain at peace with their neighbors. However this policy had now backfired disastrously.*

*Lodovico Manin, had in this regard, been the most neglectful of all the recent Doges, and his dealing with the young twenty six year old unknown French General sweeping all the armies of Europe before him had been nothing short of insipid in the extreme. It was now when Venice faced the greatest threat in her history, that the strongest leadership was required. Neutrality is, or rather can be, a perfectly respectable policy, but as one Venetian official, Francesco Pesaro pointed out, neutrality only works from a position of strength...not weakness. By 1795 the once great Venetian navy was less than a shadow of its former self. The glory days of Lepanto and the Fourth Crusade were now only the dimmest of memories. In order to placate Pesaro, the Senate ordered the fleet to come up from Corfu, then without explanation, quietly revoked the order. The truth was, that by a policy of neglect, and total indifference, there wasn't a Venetian navy anymore. The*

*Senate commissioned the Admiral for Home Waters, seventy six year old, Giacomo Nani, to provide a report on the state of the Venetian navy. His report proved so damning, that it was clear that Venice could not count on it to defend the lagoon. Only four galleys and seven galleots were even partially ready for service, and even so these vessels were obsolete. Against the modern French navy, that would in a decade be able to challenge the British Fleet on the high seas, there wasn't even a hope.*

*The magisterial John Julius Norwich, in his superlative "History of Venice", explained the situation thus:*

*"When Lodovico Manin, the 118th Doge of Venice and the last, was elected by twenty eight votes to thirteen on 9 May, 1789, he and his subjects were still unaware that, only four days previously, the States General of France had met at Versailles and that the chain of events had already begun that was to bring France to revolution. It is not likely, however, even if the news had reached the Rialto, that the Venetians would have paid it much heed. For over seventy years now they had lived in an ivory tower, secure in the belief that their by now traditional policy of neutrality would save them from all ills and that their determination to live in peace with their neighbours would be universally respected. Their mistake - the most tragic mistake in all their history - was to cling to this belief long after they should have seen it to be untenable; and for this disastrous piece of self-deception Lodovico Manin must bear much of the responsibility....."*

*Manin's career in public life had been distinguished enough, but not unusually impressive....in marked contrast his predecessor, he was at least honest; even in the worst days that lay ahead, his integrity was never questioned. But in the years during which he was called upon to guide the Republic, there were other qualities more important than even honesty; strength, vision, courage, firmness of will. Of these particular qualities Lodovico Manin seems to have possessed scarcely a trace, indeed as one reads through the last painful records of the dying Republic, one is tempted to wonder whether they had not disappeared altogether from Venice...."*

*Since the fall of the Western Roman Empire, and up until the time of Italian reunification over fourteen centuries later, Italy had been the battle ground upon which other nations, states, and empires had fought. In 1795 France was fighting the Austrian Empire. Following the revolution most of Europe had sided together in order to bring down the godless regicides who threatened the divine rights of monarchies. Much to everyone's astonishment however, the new French Citizen Armies, fired with Revolutionary fervor, were holding off the combined efforts of the First Coalition. The Prussians had been decisively defeated at the famous Battle of Valmy, and now a twenty six year old general, named Napoleon Bonaparte was sweeping all Austrian Armies before him, across northern Italy. Although Venetians professed neutrality, they had pinned their hopes on Austria to defend them against the aggressions of the new republic. Indeed Venice gave covert support to Austria, which infuriated the French. The Directory in Paris perhaps cognizant of the fact that it had not a single friend or ally, offered Venice an alliance on no less than three separate occasions - the first, offered by Napoleon himself in Brescia on 21 August. But each time Venice refused. Although a republic itself, Venice saw France as a nation of anarchists and regicides. But Norwich suspects that other less honorable factors were also at play. Venice had simply forgotten how to fight. With the*

*Napoleonic army now on its doorstep, the Venetians were so terrified of the thought of war, that any other prospect - even annihilation - was unthinkable.*

*By rejecting Bonaparte's overtures, they convinced him not only of their hostility, but much worse; they had delivered a blow to his pride. This decision, Norwich explains, was suicidal, and the moment that Venice took it, her death warrant was signed. When Mantua fell on 2 February 1797, the last Austrian resistance to Napoleon collapsed. Disaster then struck when Italian nationals, none too eager to embrace the new Enlightenment and Revolutionary ideals rose up against the occupying French. Verona was Venetian city. This was the last straw. Napoleon sent his aide - de - camp General Junot with what amounted to a declaration of war. All the Venetian senate could come up with was a cringing letter of apology for what had happened in Verona.*

*The Senate in a panic sent two high level envoys to plead with Napoleon. Although he did receive them, it was all they could do to simply appease his mounting fury. But by now he was past listening; Norwich continues:*

*“Striding backwards and forwards across the room, the speed and volume of his heavily accented Corsican Italian increasing with every step, he launched into a searing diatribe against Venice, her government, and her people, accusing them of perfidy, hypocrisy, incompetence, injustice and - most serious of all in his eyes - hostility to himself and to France, ending with the words that soon were to echo in the heart of every Venetian, “I will have no more Inquisitions, no more Senate - I shall be an Attila to the State of Venice!”.*

*If Venice at its greatest hour of need had had an Enrico Dandolo, a Francesco Foscari or a Leonardo Dona leading Venice, perhaps an alliance with Austria, Naples and Sardinia, and with a few as 25,000 well led troops, the French army may yet, even at this eleventh hour, been pushed out of Italy. But this would also be to underestimate the brilliance of Napoleon as a battlefield general. But none of this happened. When the emissaries returned to Venice, the only hope lay in total capitulation to Napoleon's terms; either that or face the fury of the French Army and the destruction of their incomparable city. The terms were terrible indeed - nothing less than the abdication of the Doge and the ruling oligarchy, and the dissolution of the constitution that had stood for a thousand years, to be replaced by a “democracy” under French rule. If the Senate were expecting a stirring speech of leadership and defiance from their Doge, they were sorely disappointed. Lodovico, wringing his hands, and pacing up and down, simply muttered the unedifying words that he would never be able to live down for the rest of his life; “Tonight there will be no safety for us, not even in our own beds”. Francesco Pesaro announced a somewhat more pragmatic course of action for himself, that many would emulate - immediate flight to Switzerland*

*Lodovico called the Great Council on May 12, to deliver the news to the people of Venice's capitulation to Napoleon. A great crowd began to gather in the piazza of St. Marks as they had done countless times before, but those times were mostly for celebration or to express some dissatisfaction with some or other affair. This time was different. With the French army massing on the mainland across from the lagoon the people were congregating out of terror. To give encouragement to the Council, there*

were half hearted sorrowful calls of “Viva San Marco!” In the grand Council Lodovico delivered Bonaparte’s terms and proposed a motion of acceptance, “with the most high object of preserving unharmed the Religion, life and property of all these most beloved inhabitants” As gunshots were heard in the distance, the niceties of protocol and debate were abandoned amidst panicked cries of “Vote! Vote!”. The final count, though few remained to hear it after hurriedly casting their vote and fleeing, was 512 in favor of the resolution, twenty against and five abstentions. To a virtually empty hall, Doge Manin declared the resolution adopted. Thus the brilliant thousand year reign of the Venetian Republic came to an end.

Lodovico himself made no effort to flee. In the silence that followed, he gathered up his papers and went to his private apartments, where he laid aside his ducal corno, and various robes of office. He handed his cuffietta to his valet with the words that echoed the whole sad demise of Venice, “Take it. I shall not be needing it again”.

At the subsequent treaty of Campo Formio, Napoleon dismantled the Venetian territories dividing the spoils between France and a subdued Austria. Venice itself went to Austria and became part of the Austrian Empire on the 18th of January 1798. Norwich’s poignant conclusion to the whole sad affair was that the great tragedy was not so much the fact that the Venetian Republic came to an end, all empires eventually do, but rather it was the whimpering manner in which it did so, given its glorious history and its unsurpassed longevity. At least for the Byzantines there was always the glorious memory of its last Emperor Constantine XI, fighting heroically, sword in hand among his people on the ramparts of the great city of Constantine. The Venetian Republic in bleak contrast committed suicide by a panicked process of administrative procedure.

Following his abdication Lodovico remained in Venice, living in seclusion and refusing to answer his door, even to close friends. He developed dropsy in his final widowed years and in an effort to remain active and try to prolong his life he would try to take short walks, but would invariably be subjected to insults and derision by the citizens who blamed him for the fall of the Republic. He died of his dropsy in 1802 at the age of seventy seven.

Dropsy, or cardiac failure, remains a leading cause of death over two centuries following the death of the last Doge of Venice. Lodovico perhaps was showing an admirable proactiveness in attending to his health in his old age, a quality he had so sadly lacked during his tenure as Doge. In the 21st century a host of modern drugs, such as the ACE inhibitors are now available for treatment of the dropsy. The situation however remains problematic. As for the Most Serene Republic in the final years of the Eighteenth century, we may still have a chance for prolongation of survival, if we make the right choices, but as the damage has already been done, the end result sadly nonetheless, remains all too inevitable.

## RAMIPRIL

### Introduction

**Ramipril** is an **angiotensin converting enzyme inhibitor (ACE Inhibitor)**.

It is a **prodrug** that is converted in the body into an **active metabolite - ramiprilat**

**It essentially has the same indications, contraindication and adverse effects profile of all the ACE inhibitors.**

The ACE inhibitors, as a class, have clinical utility in:

1. Hypertension:
2. Heart failure:
3. Post myocardial infarction
4. Reduction of cardiac disease risk **irrespective** of blood pressure level before treatment.
5. Some renal disease

Its principle adverse effects include:

1. Hypotension
2. Angioedema
3. Hyperkalemia

**See also separate documents on:**

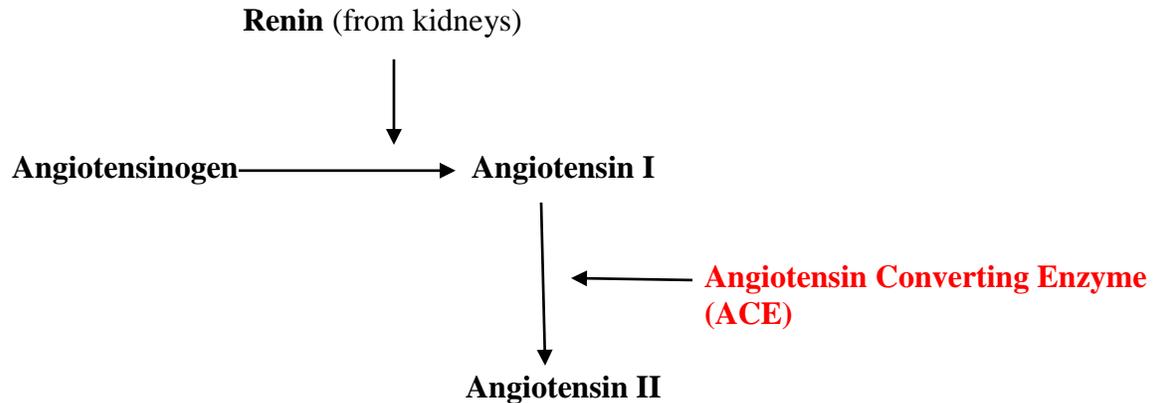
- **ACEI Overdose (in Toxicology folder).**
- **Angioedema (in Allergies folder).**

### History

**Captopril** was the first ACE inhibitor developed for clinical use. It was synthesized in 1975 by three researchers, Miguel Ondetti, Bernard Rubin, and David Cushman at the U.S. drug company Squibb.

The development of captopril in the 1960s (and all subsequent ACE inhibitors and sartans) grew out of intense research into the hypotension inducing effects of the **Brazilian Pit Viper snake**, which contains a powerful ACE inhibiting factor!

## Physiology



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

Renin, is an enzyme synthesized by the kidneys, into the circulation in response to hypotension.

Renin acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide.

Angiotensin I is then converted enzymatically by **angiotensin converting enzyme (ACE)** to the octapeptide **angiotensin II**. The conversion of angiotensin I to angiotensin II takes place in the pulmonary circulation (rather than the plasma).

Angiotensin II has the following actions:

- It is a potent arteriolar **vasoconstrictor**
- It stimulates **aldosterone** secretion from the adrenal cortex, thereby contributing to **sodium** (and so fluid) retention and potassium loss.

## 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

Supposed advantages for specific ACE inhibitors are claimed based on pharmacokinetic, metabolic or tissue ACE-binding characteristics, however, these do not translate into significant clinical differences. <sup>2</sup>

### Preparations

Ramipril as:

Tablets:

- 1.25 mg, 2.5 mg, 5 mg, 10mg.

Fixed dose combinations:

- Fixed dose combinations with felodipine are also available.

### Mechanism of Action

The ACE inhibitors:

1. Inhibit the action of ACE:

- They are highly specific competitive inhibitors of angiotensin I converting enzyme, (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II.

2. Inhibit the breakdown of bradykinin, (see **Appendix 1**)

### Pharmacodynamics

In single dose studies, doses of 5-20 mg of ramipril lowered blood pressure within 1-2 hours.

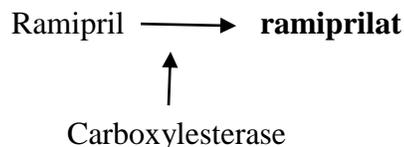
Peak reductions are achieved 3-6 hours after dosing.

The antihypertensive effect of a single dose persists for 24 hours.

### Pharmacokinetics

#### Absorption:

- Ramipril administered orally.
- The extent of absorption is at least 50 - 60 %.
- Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, **ramiprilat**



#### Distribution:

- The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%.
- Ramipril can cross the human placenta
- It is unknown if ramipril is excreted into human breast milk.

#### Metabolism and excretion:

- Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, **ramiprilat**

Ramipril is almost completely metabolized to ramiprilat, (which has about 6 times the ACE inhibitory activity of ramipril), and to the diketopiperazine ester

- After oral administration of ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine, and about 40% is excreted via the GUT.

Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

- The elimination half life is long at > 50 hours.

### Indications

As a class the ACE inhibitors are used for: <sup>2</sup>

1. Hypertension:

- Used as standard treatment, often in combination with other agents.

2. Heart failure:

- Angiotensin converting enzyme inhibitors (ACEI) are particularly useful in patients with systolic (and probably diastolic) dysfunction. <sup>1</sup>
- They are frequently used in combination with a diuretic in patients with symptomatic heart failure.

3. Post Myocardial infarct:

- In patients with left ventricular dysfunction.

ACE inhibitors are indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction, manifested as an ejection fraction less than or equal to 40%, and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients. <sup>3</sup>

4. Reduction of cardiac disease risk:

- ACEI decrease cardiovascular disease (CVD) risk in patients with established CVD or high absolute CVD risk due to multiple risk factors (particularly hypertension and diabetes), **irrespective** of blood pressure level before treatment.

5. Some renal disease:

- Diabetic nephropathy (type 1 diabetes)
- Prevention of progressive renal failure in patients with persistent proteinuria (> 1 gram daily).

## Contra-indications/precautions

These include:

1. History of hypersensitivity to captopril
2. History of angioedema:
  - This can be hereditary, idiopathic or ACE inhibitor-induced. ACE inhibitors increase risk of further episodes.
3. Hypotension
4. Hyperkalemia, (which can also be a side effect)
5. Volume or sodium depletion:
  - This activates the renin - angiotensin - aldosterone system.  
  
Initiation of an ACE inhibitor this may result in excessive hypotension. Correct before treatment and/or monitor carefully.
6. Caution with other drugs that can raise potassium levels:
  - Potassium supplements and potassium sparing diuretics (use only with **caution** and **close monitoring**).
7. Primary hyperaldosteronism:
  - An ACE inhibitor may have reduced effectiveness or be ineffective; seek specialist advice.
8. Patients with renal artery stenosis:
  - The risk of renal failure is increased, (especially if bilateral).
9. Renal impairment:

Use with caution and monitor closely:

*As a guide:* <sup>2</sup>

Renal impairment increases risk of hyperkalaemia and may affect the excretion of some ACE inhibitors; use lower initial doses and monitor potassium concentration.

Renal impairment 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 ACE inhibitor and consider specialist referral.

10. 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.

11. Pregnancy, (contraindicated): <sup>1,4</sup>

- When pregnancy is suspected, treatment with ACE inhibitors should be discontinued immediately and changing to an alternative antihypertensive, such as methyldopa or labetalol, (see below).

### Pregnancy

Ramipril is classed as a category D 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.

One study has concluded that exposure to angiotensin-converting enzyme (ACE) inhibitors during the first trimester could possibly increase the risk of congenital malformations and should be avoided. However, most studies have shown that exposure to ACE inhibitors in the first trimester have not been associated with an increased risk of major malformations compared with other anti-hypertensives; but a slight increase was noted when compared with healthy controls.

Maternal exposure to ACE inhibitors in the second and third trimester have been associated with adverse fetal effects such as oligohydramnios, severe fetal growth restriction, persistent patent ductus arteriosus, pulmonary hypoplasia, limb contractures, renal tubular dysgenesis and fetal or neonatal death.

**When pregnancy is suspected, treatment with ACE inhibitors should be discontinued immediately and changing to an alternative anti-hypertensive, 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, should be offered to women who have taken an ACE inhibitor during the first trimester.

### Breast feeding:

Reports describing the use ramipril during breastfeeding have not been located, and the effects on the breastfed infant are unknown. Therefore, consider an alternative medicine where possible.

Shorter 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. Hypotension:

- Including **postural hypotension**.

This most commonly occurs in patients:

- ♥ Commencing treatment (**first dose** in particular).
- ♥ Who are taking other antihypertensive agents.
- ♥ Who have *severe* congestive heart failure

2. Cough: <sup>2</sup>

- A persistent, nonproductive cough is common, possibly due to a bradykinin effect.

It is not dose-dependent

It is unlikely to respond to treatment.

It can occur within days to months of starting treatment.

The cough may be mild and tolerable, however, some patients need to stop treatment (usually then improves within 1- 4 weeks of stopping).

Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

3. Angioedema:

- This is usually mild to moderate, but can occasionally be life-threatening.

It is thought to be due to bradykinin build up.

Icatibant can be used to treat it.

4. Hyperkalemia:

- Because the ACE inhibitors decrease the formation of angiotensin II and the subsequent production of aldosterone, serum potassium concentrations exceeding 5.5 mEq/L may occur.

Frank hyperkalaemia may occur in patients who have impaired renal function and/ or are taking other agents that can elevate the serum potassium levels and /or are diabetics.

5. Dermatological hypersensitivity reactions.

**Dosing**<sup>2</sup>

Always commence with a **low** dose; naive patients can suffer significant hypotension.

**Hypertension:**

- *Adult*, 2.5 mg once daily, increase after 2–3 weeks to 5 mg if necessary. Maximum 10 mg daily in 1 or 2 doses.

**Fixed-dose combination with felodipine**

- *Adult*, 1 tablet once daily (of either strength).

**Heart failure:**

- *Adult*, initially 2.5 mg twice daily, beginning 2 - 10 days after MI in patients who are haemodynamically stable; increase at intervals of 1 - 3 days up to 10 mg daily in 2 doses.

**Increased cardiovascular risk:**

- *Adult*, initially 2.5 mg once daily, increase after 1 week to 5 mg once daily and after 3 weeks to 10 mg once daily.

**Renal impairment, elderly or taking a diuretic:**

- *Adult*, initially 1.25 mg once daily.

Proteinuria:

- *Adult*, initially 1.25 mg once daily, double at intervals of 2 - 3 weeks, depending on tolerance, up to 5 mg once daily.

Monitoring:

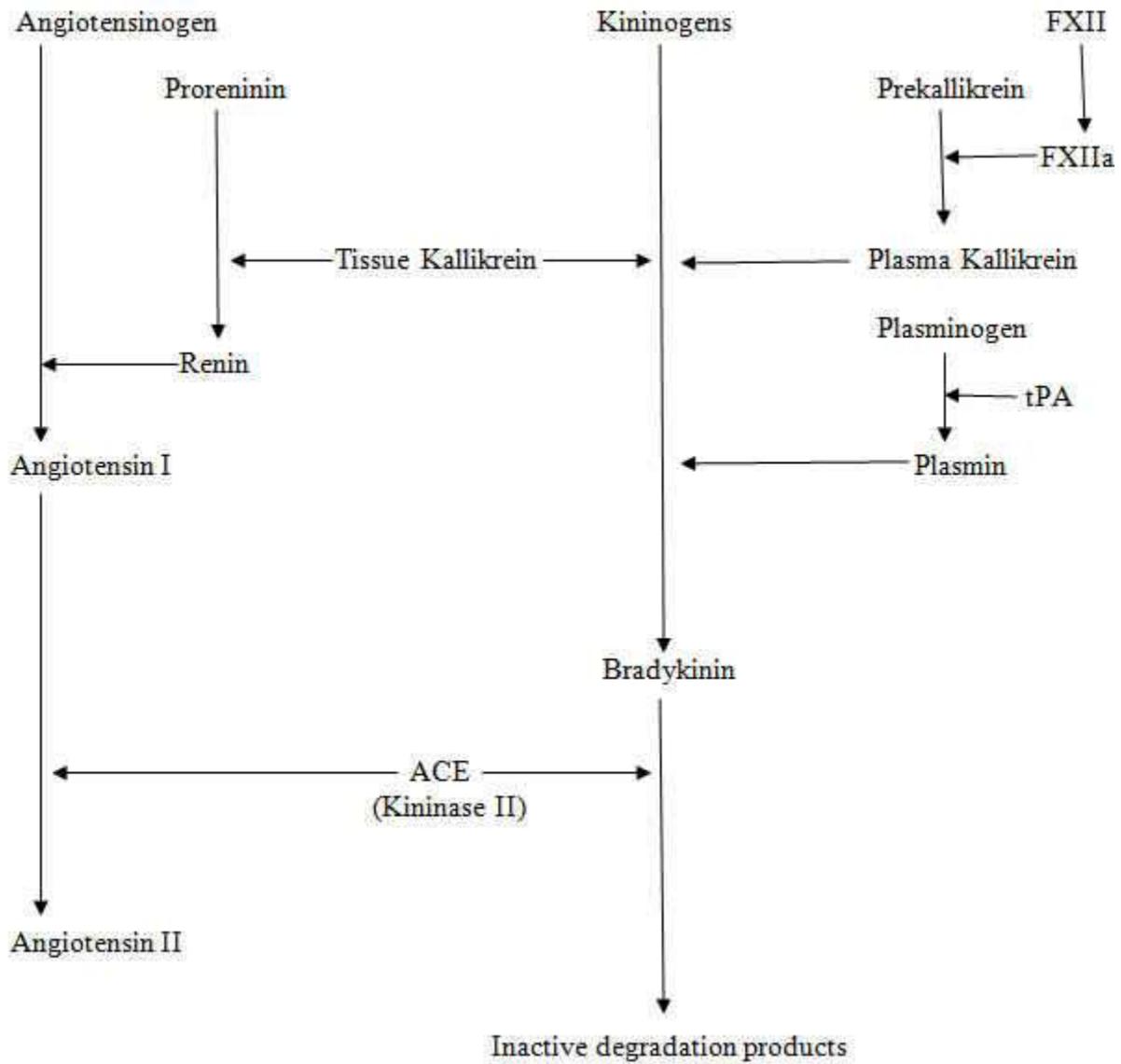
Check renal function and electrolytes before starting an ACE inhibitor and review after 1 - 2 weeks of treatment.

Note on concomitant treatment with sartans:

Treatment with an **ACE inhibitor and a sartan:** <sup>2</sup>

- 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 be an option, e.g. for **selected** patients with chronic heart failure or non-responsive blood pressure, **seek specialist advice.**

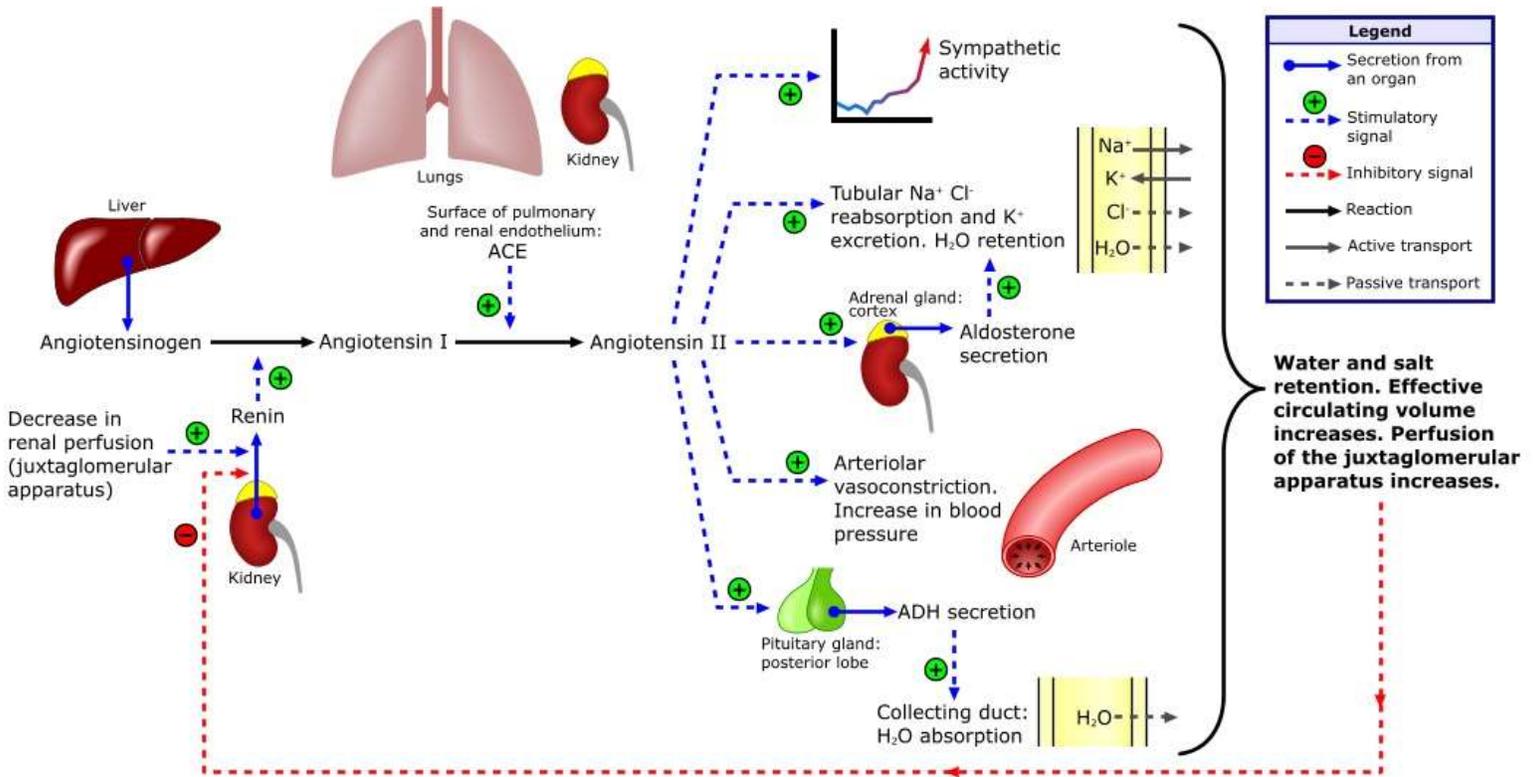
## Appendix 1



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

## Appendix 2

### The Renin - Angiotensin - Aldosterone System:





*Jean Andoche Junot oil on canvas, 1792 Henri Félix Emmanuel Philippoteaux, salle 1792, Palace of Versailles*

*“I send you my principal aide - de - camp as bearer of the letter. Is it to be war or peace?”*



*Tomb of Lodovico Manin, Santa Maria degli Scalzi, Venice*

*Postscript:*

*Only one thing can be said of Lodovico Manin and those sad, feckless men who presided with him over her downfall. By their craven surrender they did at least ensure the preservation of their city. Had the French artillery been induced to open fire from its*

*emplacements on the mainland shore, had French warships found it necessary to enter the lagoon and bombard Venice from the water, one dare not imagine what the consequences might have been. Even as things turned out, much was lost. On the flimsiest of pretexts, Bonaparte gave orders for the seizure of pictures, sculptures, manuscripts, church plate and all the priceless works of art his specially appointed Commissioners could lay their hands on, including even the four bronze horses of St. Mark which were shipped off to Paris to adorn the Arc du Carrousel in the Tuileries gardens. The horses, as we know, were later restored to the gallery of the Basilica, (at the time of writing they are in the course of being removed inside, victims of the atmospheric pollution that is taking a more terrible toll of Venetian sculpture than Napoleon ever did), but much of the conqueror's loot, including Veronese's tremendous "Marriage of Cana" from the Refectory of S. Giorgio Maggiore, and his central panel from the ceiling of the Council of the Ten in the Doge's palace, is still in the Louvre - and likely to remain there. We can only be thankful that Bonaparte himself, astonishingly enough, never set foot in Venice. Had he done so, there is no telling how much more thoroughly he would have despoiled the most opulent of all cities, or how much deeper would have been the scar that even his shadow was able to leave behind.....*

*John Julius Norwich, "A History of Venice".*

### References

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2. Ramipril in Australian Medicines Handbook Website, Accessed April 2019.
3. Ramipril in MIMs Website, 1 December 2012.
4. Ramipril in RWH Pregnancy & Breastfeeding Guidelines; 15 December 2017.

Dr J. Hayes.

Reviewed April 2019.