Antihypertensives: ACE-Inhibitors and Sartans

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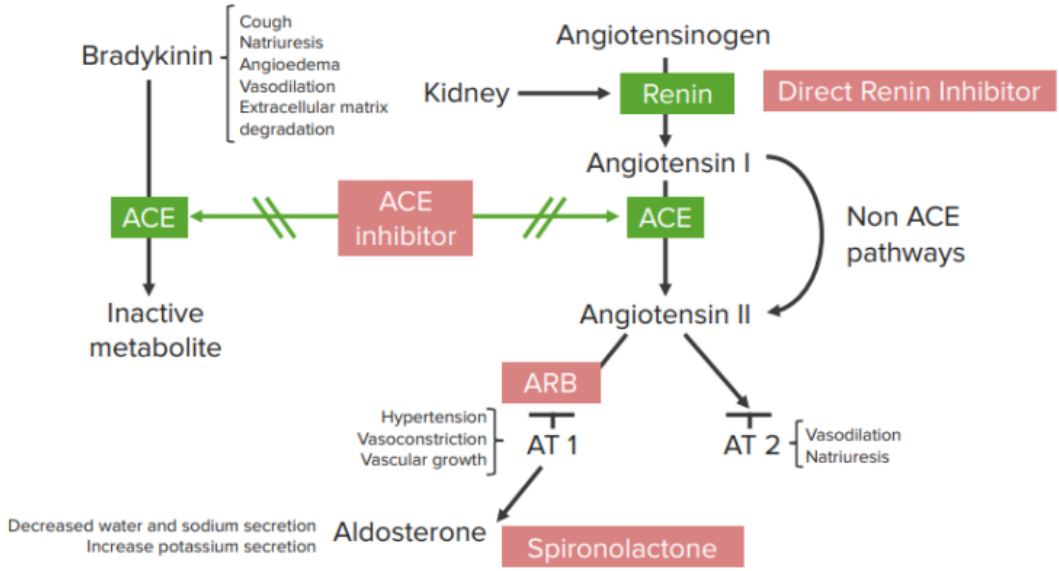
Arterial hypertension can often be reduced with general measures; however, medicinal approaches are also advisable in order to reach target blood pressures and bring them within the normal range. The most commonly prescribed drugs are ACE-inhibitors, as they are inexpensive, followed by sartans. Both substances reduce blood pressure by affecting the renin-angiotensin-aldosterone system (RAAS).

The Angiotensin-Converting Enzyme Inhibitors



Renin Angiotensin Aldosterone Pathway (RAAS). Image by Lecturio

Overview over ACE-inhibitors

Most ACE-inhibitors are prodrugs, which are activated by esterases in the liver after enteric resorption. The most effective ones are:

- Benazepril
- Cilazapril
- Enalapril (moderate to long half-life period, so ingestion must be twice a day)
- Fosinopril
- Moexipril
- Perindopril
- Quinapril
- Ramipril (today’s cheapest antihypertensive; long half-life period)
- Spirapril
- Trandolapril

The only two ACE-inhibitors that are not prodrugs (do not need activation) are

- Captopril (shortly active, only suitable for the initial adjustment)
- Lisinopril (long half-life period)

Effects of ACE-inhibitors

ACE-inhibitors inhibit the angiotensin-converting enzyme (ACE), resulting in less angiotensin I being converted to angiotensin II (the active form). With less angiotensin II (a powerful vasoconstrictor), the effects are decreased vasoconstriction, afterload, and blood pressure.

Furthermore, the production of aldosterone is decreased due to the decreased angiotensin II, so that less sodium and water are reabsorbed in the kidney, and diuresis takes place. This decreases total body water and edema (if present). The excretion of potassium is also decreased.

The decreased angiotensin II concentration also reduces excretion of epinephrine and

norepinephrine from sympathetic nerve endings and the adrenal medulla via AT1 receptors, thereby inhibiting the sympathetic nervous system. This effect on blood pressure reduction is controversial.

Normally, ACE not only acts on angiotensin I, but it is also a kinase, which inactivates bradykinin, kallidin, and substance P. If ACE is inhibited, the concentrations of these peptides will rise and promote excretion of nitric oxide and prostacyclin out of the endothelium, which in turn vasodilate. This contributes to blood pressure reduction.

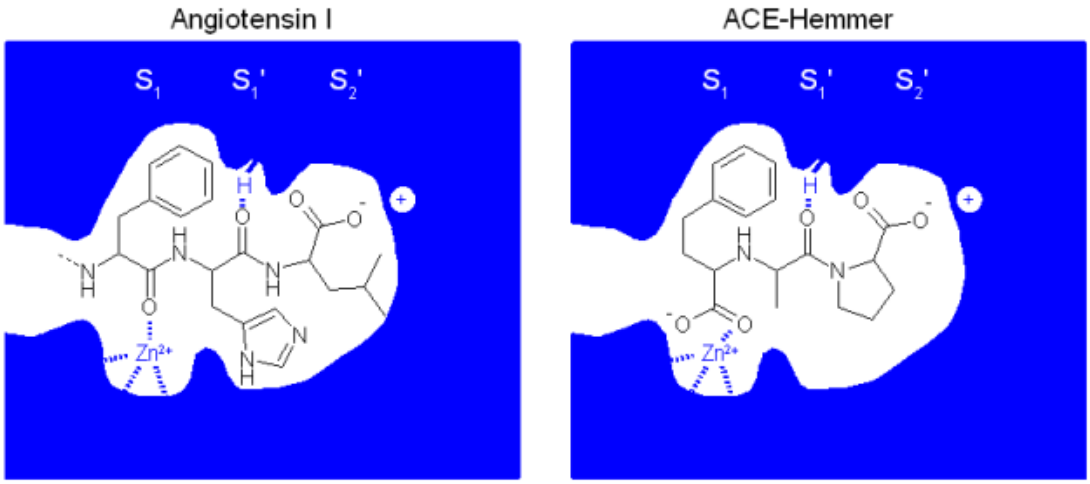


Image: “Molecular mechanism of action of ACE inhibitors (=ACE-Hemmer)” by Sven Jähnichen. License: CC BY-SA 3.0

The increase of bradykinin in the myocardium also has a **cardioprotective effect.** Growth appears to be inhibited in both the heart and the vessels, which leads to reduced mortality during ACE inhibitor treatment. A **renal protective effect** is significant during ACE inhibitor treatment as well. The efferent arterioles of the kidneys are vasodilated and the glomerular filtration rate is decreased, reducing pressure in the glomeruli.

Adverse effects of ACE inhibitors

The most important adverse effects of ACE inhibitors are **a dry cough** (probably due to the increase of substance P), which in many cases leads to discontinuation of treatment, **angioedema, and hyperkalemia.** Hyperkalemia occurs most often when ACE inhibitors are used in combination with aldosterone receptor antagonists or potassium-sparing diuretics, as well as in patients with renal insufficiency or diabetes mellitus.

Initial dosage should be titrated up to **avoid excessive blood pressure reduction (hypotension).** Other possible adverse effects are **nausea and headache**, as well as allergic **exanthemata.** An **increase of creatinine** can occur, which is not problematic when increased by up to 30%, but if the level is higher, renal artery stenosis may be suspected.

Indications for the use of ACE-inhibitors

ACE inhibitors are used for the treatment of **primary arterial hypertension** and are the treatment of choice with accompanying heart failure and renal insufficiency. Administration of ACE inhibitors is also indicated after a myocardial infarction (2–7 days post-infarction). ACE inhibitors are often prescribed with accompanying diabetes mellitus or metabolic syndromes, as they are metabolically neutral.

Contraindications of ACE inhibitors

The most important contraindications for the use of ACE inhibitors are **renal artery stenosis** or **severe renal insufficiency** (with creatinine > 3 mg/dL). Other contraindications are **aortic stenosis** and **pregnancy.**

Substance	Effect duration (in hours)	Mean antihypertensive dosage (in mg/dl)
Captopril	8–12	2–3 x 12,5–50
Ramipril	24–48	1 x 2,5–5
Enalapril	12–24	1–2 x 5–10
Fosinopril	24	1 x 10–20
Lisinopril	24	1 x 5–10
Quinapril	12–24	1–2 x 10

Angiotensin II Receptor Blockers (ATII Blockers)

Overview

Angiotensin II receptor antagonists or blockers create effects similar to ACE inhibitors, but they are not the first treatment of choice due to high costs. The most common ones are:

- Losartan
- Valsartan
- Candesartan
- Eprosartan
- Irbesartan
- Olmesartan
- Telmisartan

Mechanism of action and effect of ATII blockers

The effects of ATII blockers resemble those of ACE inhibitors, as they also prevent the effects of angiotensin II, but instead of inhibiting the production of ATII (ACE), they inhibit binding of ATII to its receptors. This also results in vasodilation, decreased aldosterone production, reduced sodium and water reabsorption, and diuresis.

Like ACE inhibitors, blood pressure is reduced, and cardiac insufficiency can be improved. There is also a renal protective effect. Unlike ACE inhibitors, the effects on the bradykinin metabolism are absent because ACE is still active with ATII blocker therapy.

Adverse effects of ATII blockers

The adverse effects are similar to those of ACE inhibitors, especially hyperkalemia. Angioedema occurs less than with ACE inhibitor treatment. Another advantage of ACE inhibitors is less incidence of dry cough.

Indications for the use of Angiotensin II blockers

Like ACE inhibitors, Angiotensin II blockers are used for the treatment of arterial hypertension. They can also be used for chronic cardiac insufficiency. Angiotensin II blockers are normally used in patients that are intolerant of ACE inhibitors (usual patients

with a cough due to ACE inhibitor use).

Contraindications of Angiotensin II blockers

Contraindications for treatment with Angiotensin II blockers include renal artery stenosis, renal insufficiency, aortic stenosis, and pregnancy.

Dosage for Angiotensin II blockers

Substance	Effect duration (in hours)	Mean antihypertensive dosage (in mg/dl)
Candesartan cilexetil	≈ 24	1 x 4–16
Irbesartan	≈ 24	1 x 150–300
losartan	< 24	1–2 x 50
Olmesartan medoxomil	≈ 24	1 x 10–20
Telmisartan	> 24	1 x 20–80
Valsartan	≈ 24	1 x 80–160

References

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Notes