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## Transparency review of pharmaceutical administration and policies

The second government of Finnish Prime Minister Matti Vanhanen is currently extensively reorganising the government administration and its structures. Central administration is being reorganised by transferring executive responsibilities from the ministries down to lower levels of administration. The responsibilities of the ministries and the national boards will be clearly distinguished, and the responsibilities of the national boards will be reassessed. The government first successfully demonstrated its capacity for reorganisation by creating the new Ministry of Employment and the Economy (MEE) in record time. The government is involved in development and reorganisation projects in almost all administrative areas.

Far-reaching development projects are also underway in the Ministry of Social Affairs and Health, from the Ministry itself right through to the various agencies and institutions. The Ministry's new organisational structure came into effect at the beginning of May. In addition to these projects, work is also being carried out to improve transparency in the fields of pharmaceutical administration and policy.

No administration or bureaucracy is an end in itself. Thus from time to time it is entirely appropriate to review and restructure an administration, and adjust the way in which policies are managed and coordinated. This has not happened in the pharmaceutical sector since the beginning of the 1990's, when the structures governing the present administration and activities were created. Since that time, Finland has reached the historic landmark of EU membership, and pharmaceutical and medical devices regulation has been Europeanised.

Good decisions need to be preceded by good reviews and proposals. On this occasion, the Ministry of Social Affairs and Health has decided to turn to Professor Jussi Huttunen, a highly experienced expert in review issues, for assistance in the development of pharmaceutical administration. By invitation at the beginning of February, Professor Huttunen was given a review task on how best to redirect resources and improve the activities and working methods of NAM and the Centre for Pharmacotherapy Development, and, with regard to pharmaceutical administration, of the National Research and Development Centre for Welfare and Health (STAKES) and the National Public Health Institute. It was also request-

ed that a review be carried out of the involvement of the Social Insurance Institution in the assessment of the therapeutic value of drugs. Professor Huttunen submitted an interim report on this at the end of March, which was followed by a consultation round. In its statement, NAM emphasised the importance of consolidating resources, expert advice and administration<sup>1</sup>.

The third item under review was the responsibilities borne by the Ministry of Social Affairs and Health and by the Drug Pricing Board with regard to pharmaceutical issues. The deadline for this part of the review (final report) was at the end of May. In addition to his involvement in the issues under review described above, Professor Huttunen, in his capacity as a reviewer of the administration of pharmaceutical policies, was also invited to become a member of the lead group for the project developing the structure and activities of the Ministry. One of the aims of this project, which will end in October, is to improve strategic activities in this area of administration, and to develop the NAM guidelines.

Not only Finnish bodies have been involved in evaluating and reviewing Finland's pharmaceutical policies. Even during the previous government, the Ministry of Social Affairs and Health invited Professor Elias Mossialos from the London School of Economics to review the problems faced and options available with regard to pharmaceutical policy in Finland. This report was published in March this year<sup>2</sup>. Key observations from the report include deficiencies with regard to the coordination of pharmaceutical policies, and inadequate expertise.

At last, adequate efforts have been made to review the situation. Concrete guidelines and principles are now needed for the future development of pharmaceutical administration and policy. NAM hopes that the solutions will take into account the challenges anticipated in the 2010's, and will be based on effective leading principles in pharmaceutical administration.

<sup>1</sup> [http://www.laakelaitos.fi/instancedata/prime\\_product\\_julkaisu/laakelaitos/embeds/Ajankohtaista\\_Lausunnot\\_LL\\_Lausunto\\_valiraportista\\_180408.pdf](http://www.laakelaitos.fi/instancedata/prime_product_julkaisu/laakelaitos/embeds/Ajankohtaista_Lausunnot_LL_Lausunto_valiraportista_180408.pdf)

<sup>2</sup> Mossialos E & Srivastava D. Pharmaceutical Policies in Finland. Challenges and opportunities. <http://www.euro.who.int/Document/E91239.pdf>



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## Treatment and prognosis for SLE

*Systemic lupus erythematosus* (SLE) is a connective tissue disease with widely varying symptoms. They may vary from very mild skin and joint symptoms to severe organ damage such as kidney and central nervous system symptoms. The periodic character of the stages of activity are also typical of the disease. SLE is an example of a connective tissue disease with a number of associ-

ated immunological abnormalities, e.g. the production of antibodies and immune complexes and tissue damage resulting from immunological disorders (1). The diagnosis of SLE is based on the updated classification criteria of the American College of Rheumatology (ACR) of the year 1997 (Table 1). A minimum of four out of the 11 criteria are necessary for the diagnosis of SLE.

term use also prevents permanent organ damage caused by SLE in the patients and improves the prognosis for survival (9, 10). In a Spanish follow-up study (11) SLE patients on anti-malarial medication were, during a 10-year follow-up period, found to have fewer malignancies in comparison with the control group.

### Methotrexate and azathioprine

Methotrexate is often also used in the treatment of mild and moderate SLE symptoms. There are several non-randomised studies on the use of methotrexate in SLE with proven response especially in skin and joint symptoms (12). Methotrexate therapy can also be used in the treatment of other SLE symptoms, those of myositis and serositis, for example (13, 14). In two randomised studies (15, 16) methotrexate therapy reduced the general disease activity in SLE patients in comparison with placebo. The daily dose of prednisone was also smaller in the group receiving the actual drug in comparison with the placebo group.

Azathioprine is probably the most common immunosuppressive drug used as a corticosteroid-sparing therapy in the treatment of SLE. Azathioprine is generally not used at the acute stage of the disease, it is instead a primary drug for many SLE patients who have recurrent activation stages and a need for increased doses of corticosteroids.

Table 1. Classification criteria for SLE (ACR 1997)

1. Butterfly rash
2. Lupus discoides
3. Photosensitivity
4. Ulcers of the oral mucosa
5. Arthritis
6. Serositis (e.g. pleuritis, pericarditis)
7. Kidney damage (recurring proteinuria > 0.5 g/day or cell casts)
8. Neurological symptoms (e.g. epileptic seizure, psychosis)
9. Haematological abnormality (haemolytic anaemia, leukopenia or lymphopenia at least twice, thrombocytopenia)
10. Immunological abnormality (DNA-antibodies, Sm-antibodies or phospholipid antibodies)
11. Positive antinuclear antibody

### Hydroxychloroquine

Hydroxychloroquine (HCQ) has been the primary drug in the treatment of SLE for a long time, used especially in the treatment of the milder symptoms of the disease, such as skin and joint symptoms, treatment of serositis and mild haematological changes (1). The mechanisms of action of the drug are not fully known, but it has been proven to decrease the production of inflammation inducing cytokines, e.g. interleukin-1, interleukin-6 and tumour necrosis factor-alpha (2, 3). It reduces platelet aggregation and adhesion (4). It also has a favourable effect on the levels of lipids: HCQ reduces the levels of triglycerides and LDL (5, 6), it also has a hypoglycaemic effect (6). Several follow-up studies have been carried out examining the benefits of treatment with HCQ in SLE patients. Its long-term use has protected SLE patients against the activity stages of the disease (7, 8) and reduced the risk for thrombo-embolytic events in SLE patients (9). Long-

### Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug increasingly used in the treatment of SLE (17). It inhibits the proliferation of lymphocytes B and T and decreases the production of antibodies. It has no immunological effect on kidney cells. Experimentally it reduces the proliferation of mesangial cells. In animal models, MMF inhibits the glomerular, tubular and interstitial cell proliferation. It exerts a minor effect only on other tissues with a high degree of cell proliferation (skin, bone marrow, neutrophils). Consequently, the drug generally has fewer side effects compared with cyclophosphamide, for example. The most common side effects of MMF are intestinal symptoms: nausea, vomiting, diarrhoea. Its use is not associated with significant ovarian toxicity as with the use of cyclophosphamide therapy (17). MMF therapy has been used in a number of manifestations of SLE, such as skin symptoms, haematological changes and the treatment of nephritis, in particular. Response has also been achieved in such SLE pa-

Table 3. Management scheme for severe lupus nephritis (28)

#### Induction treatment

\* Intravenous methyl prednisolone 1 g/3 days or oral prednisone 1 mg/kg, slow reduction of dose +

#### Alternatively

\* CYC or \* MMF 2–3 g/day for 6 months.

\* Normal: 0.5–1 g/m<sup>2</sup> intravenously/month x 6 or

\* Euro-Lupus: 500 mg intravenously at 2-week intervals x 6

If no response, replaced by CYC ↔ MMF

or rituximab

#### Maintenance treatment

\* Low-dose prednisone +

\* MMF 1–2 g/day

or

\* Azathioprine 1–2 mg/kg/day

#### Supportive treatment

\* ACE inhibitor / AT II antagonist

\* Protection of the skeletal system

\* Primary and secondary prevention of cardiovascular diseases

Table 2. Classification of lupus nephritis (WHO)

- I. Normal
- II. Mesangial glomerulonephritis (GN)
- III. Focal proliferative GN
- IV. Diffuse proliferative GN
- V. Membranous GN
- VI. Sclerosing GN

tients who have not previously benefitted from other immunosuppressive therapies (18, 19).

### Lupus nephritis

Lupus nephritis is one of the most important symptoms influencing the prognosis for SLE patients (1). The WHO classification divides kidney changes into six categories (Table 2). The induction treatment established for severe proliferative lupus nephritis is intravascular corticosteroid and cyclophosphamide (CYC) pulse therapy (CYC 0.5–1g/m<sup>2</sup> and a monthly steroid for 6 months followed by pulse therapies at 3-month intervals for a to-

tal period of two years). Prolonged treatment has resulted in improved response and fewer recurrences compared with 6 months of treatment. The treatment has improved the prognosis for patients with nephritis (20, 21, 22). Nevertheless, cyclophosphamide therapy is associated with significant risks of side effects, such as leucopenia-induced problems of infection, gonadotoxicity and possible risk of malignancy (23, 24). Consequently and understandably, therapies and management programs with fewer adverse events are being investigated. In the Euro-Lupus Nephritis Trial (25) comparisons were made between a high-dose

cyclophosphamide therapy (monthly intravenous doses of 0.5–1g/m<sup>2</sup> for six months followed by two additional infusions) and lighter dosage (an intravenous dose of 500 mg at 2-week intervals administered six times). The maintenance therapy for both groups consisted of oral azathioprine. The average follow-up period was 41 months. Variations in remission (54% vs. 71%) or recurrence (29% vs. 27%) of kidney disease were not seen between the treatment groups. Patients who had received lighter treatment experienced fewer adverse events. The tendency in cyclophosphamide therapy is in fact to introduce shorter management periods and smaller cumulative drug doses.

The use of MMF in the induction treatment of severe lupus nephritis is compared with CYC therapy in four randomised studies. The number of patients treated totalled 268, with lupus nephritis of category III–IV manifested in the majority of them. In the meta-analysis (26) of these four studies, patients of the MMF group achieved remission in their kidney disease more frequently in comparison with others; the relative risk of failure of the induction treatment in the MMF management group was 0.70. Similar results in favour of the MMF group were also seen in the other endpoint events: the relative risk of end-stage kidney disease or mortality was 0.44 in comparison with the CYC management group. The studies have been carried out in patients who suffered from severe lupus nephritis with fairly intact kidney function. In the maintenance treatment of lupus nephritis, CYC therapy has been compared with azathioprine and MMF therapy (27). Overall,

azathioprine and MMF achieved superior responses and were associated with fewer side effects in comparison with maintenance treatment with CYC. Table 3 shows the present management algorithm in the treatment of severe proliferative lupus nephritis (28).

### Rituximab

Rituximab is a chimeric monoclonal antibody for B cell surface receptor CD20. Surface receptors CD20 are found in all immature and mature B cells, except plasma cells. Rituximab therapy results in a transient deficiency in B cells (29). The official therapeutic indication of rituximab is the treatment of severe rheumatoid arthritis (at a dose of 1 g intravenously every other week, administered twice) and lymphoma (375 mg/m<sup>2</sup> weekly, administered four times). Encouraged by the good results of treatment in rheumatoid arthritis, rituximab has also been tried in the treatment of SLE and other autoimmune diseases. There are a number of reports (30) on the use of rituximab in SLE patients, but not a single controlled study has been carried out. Treatment responses in severe forms of the disease have been described where no reaction to other treatments has been achieved. Good results have been described in the treatment, for example, of lupus nephritis, CNS symptoms and haematological changes and in the management of general disease activity. Rituximab does not, however, have an official therapeutic indication for the treatment of SLE. In the literature two SLE patients have been described who developed severe progressive multifocal leucoencephalopathy (PML) following

rituximab therapy. PML is a rare, severe and often fatal demyelinating disease which occurs in severely immunosuppressed patients. There is an underlying polyomavirus JC infection, which may become activated in immunosuppressed patients. Nearly

Table 4. Occurrence of neuropsychiatric symptoms of SLE (32)

#### Central nervous system

1. Aseptic meningitis
2. Cerebrovascular disease
3. Demyelinating syndrome
4. Headache (e.g. migraine, idiopathic intracranial hypertension)
5. Movement disturbances (chorea)
6. Myelopathy
7. Epileptic seizures
8. Acute confusion
9. Anxiety disorder
10. Cognitive dysfunction
11. Mood disorder
12. Psychosis

#### Peripheral nervous system

1. Acute inflammatory demyelinating polyradiculopathy (Guillain-Barré's syndrome)
2. Autonomic nervous system disorder
3. Mononeuropathy
4. Myasthenia gravis
5. Cranial neuropathy
6. Plexopathy
7. Polyneuropathy

2/3 of the cases of PML described in association with rheumatoid arthritis have occurred in SLE patients. Many of these patients have not been on high-dose immunosuppressive medication, and it is consequently suspected that SLE by itself could cause exposure to progressive multifocal leucoencephalopathy (31).

### Central nervous system lupus

About 50% of SLE patients exhibit neuropsychiatric symptoms at some stage of the disease. The neuropsychiatric symptoms of SLE manifested were classified in 1999, the classification includes a total of 19 syndromes (32) (Table 4). A fairly recent review (33) included retrospective monitoring of 41 patients with CNS lupus from 1990 to 2002. The duration of SLE which the patients had suffered was on average 5.75 years at the time of onset of the CNS symptoms. The most common symptoms included headache (54%), epileptic seizures (42%), visual disturbances (32%), tiredness (27%), hemiparesis (24%), memory disorder (24%) and confusion (24%). The CNS symptoms in 10 patients (24%) were the initial symptoms of the disease and the patients were at a later stage diagnosed with SLE. The majority of the patients (36/41) were on corticosteroid therapy. In some of the patients it was combined with immunosuppressive therapy. Some of the patients received other supportive treatment, such as antithrombotic medication or warfarin, anti-epileptic or an-

tiparkinsonian medication. At the end of the follow-up period five patients (12%) were symptom-free, 17 patients (42 %) had mild difficulties, 12 (32%) had moderate difficulties and two (5%) had severe difficulties in coping. Five patients (12%) died.

### Prognosis

Mortality among SLE patients is 3–5-fold in comparison with the rest of the population. The prognosis for patients has nevertheless significantly improved during recent decades. In the 1950's the 5-year survival rate prognosis for SLE patients was about 50%. The 10-year survival rate prognosis for the patients at present is about 80%. The most important causes of fatal outcome include the degree of severity of the disease and especially the severity of the kidney disease, infections, cardiovascular diseases and malignant tumours (1).

A prospective European follow-up study examined the causes of death of SLE patients in the years from 2000 to 2004 (34). Data of about 2,500 SLE patients from 12 centres were compiled over a period of five years. During the follow-up period 91 patients had died. The mean duration of the disease at the time of death was 10.2 years (0.1–40 years). In 1/3 of the patients the SLE was in remission at the time of death. In the rest of the patients, the severity of the disease together with organ damage contributed to the fatal outcome. In those patients who had suffered from the disease for less than five years the SLE at an active stage

contributed to the fatal outcome more often than it did in the long-term sick. The most common causes of death included infections and cardiovascular diseases. The most common infections included pneumonia and unspecified sepsis. The most common fatal cardiovascular diseases included myocardial infarction, heart failure, sudden death and ischaemic cerebral events. End-stage kidney failure was a contributing factor to the fatal outcome in 17.8% and cancer in 8% of the patients (lymphoma 3%, leukaemia 2%, solid tumour 3%).

The risk of cardiovascular diseases is increased in SLE patients. For example, the frequency of hypertension, diabetes and hypercholesterolaemia is higher than usual in SLE patients. In addition to the conventional risk factors, SLE is considered to be an independent risk factor for atherosclerosis. Long-term inflammatory diseases cause endothelial and vascular damage with subsequent exposure to the development of atherosclerosis (35). In order to improve the prognosis for SLE patients their management should be aimed at active treatment of the primary disease. The management should also focus on the conventional risk factors of atherosclerosis and associated treatment (36).

*See literature on page 7.*



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## ACE inhibitors, angiotensin receptor blockers, renin inhibitors or a combination of these in the treatment of hypertension?

The key importance of the renin-angiotensin system in the pathophysiology of cardiovascular diseases was only detected in the 1970's (1). Nowadays, among the renin-angiotensin system inhibitors, the angiotensin converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension and heart failure (2, 3). Angiotensin receptor blockers (ARBs), which inhibit the angiotensin II binding to type 1 angiotensin II (AT1) specific receptors in blood vessels and other tissues, reduce the prevalence of cardiovascular diseases, including mortality (4). The most recent group of drugs in use are renin inhibitors (1, 5–7), which specifically inhibit the cleavage of angiotensinogen to angiotensin I. (Pro)renin receptor blockers are also under development.

### Renin-angiotensin system

Plasma renin activity is a limiting factor in the rate of formation of the most important biologically active compound of the renin-angiotensin system, angiotensin II (Fig.). In the kidneys, in the walls of the afferent arterioli, there are specific smooth muscle cells (juxtaglomerular cells), which secrete renin into the blood when the

sodium balance is negative or the blood pressure is reduced. Renin breaks down angiotensinogen into angiotensin I in the blood (2, 3).

Angiotensin I (angiotensin 1–10) is transformed into a potent vasoconstrictor, angiotensin II (angiotensin 1–8) by the angiotensin converting enzyme (Fig.). Angiotensin II is further cleaved into angiotensin III (angiotensin 2–8) by aminopeptidases. Angiotensin III is biologically active and its stimulating effect on aldosterone secretion is almost as potent as that of angiotensin II, but its hypertensive effect is only one quarter of that of angiotensin II.

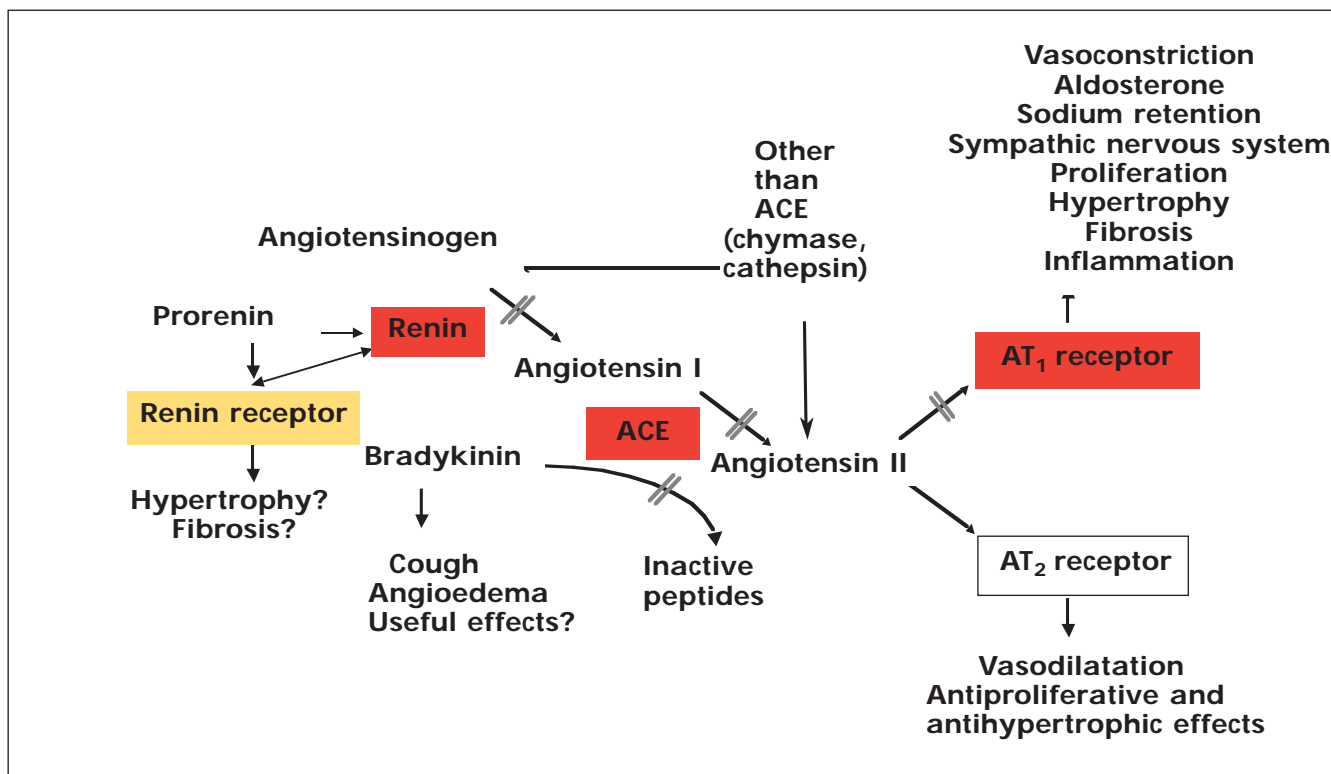
Effects of angiotensin II on the target cells are mediated via specific angiotensin receptors, of which there are two main subtypes, AT1 and AT2 receptors (2, 3). The angiotensin receptors in most tissues are mainly AT1 receptors, which mediate all the known hypertensive effects of angiotensin II. The physiological importance of AT2 receptors still remains unclear, but their number is increased in hypertrophic cardiac tissue and in hyperplastic vascular intima. Activation of AT2 receptors may actually be associated with the inhibition of

hypertrophy, fibrosis and proliferation, and with vasodilatation (2, 3) (Fig.).

### ACE inhibitors

ACE inhibitors reduce the transformation of angiotensin I to angiotensin II both systemically and locally (Fig.). Since ACE inhibitors reduce the formation of angiotensin II, renin and angiotensin I blood concentrations are increased due to the interruption of the normal feedback suppression of renin secretion. ACE inhibitors inhibit the degradation of vasodilating bradykinin and increase the formation of vasodilating prostaglandins and nitric oxide; they may promote blood pressure lowering effect and inhibition of left ventricular hypertrophy. Due to the effect of ACE inhibitors aldosterone secretion is reduced, because angiotensin II is an important regulator of aldosterone production. During ACE inhibitor therapy the formation of angiotensin 1–7 is increased, which may also partly explain the pharmacological effects of ACE inhibitors.

The most common (5–20%) adverse reaction of ACE inhibitors is a cough. It occurs more often in women compared



Renin-angiotensin system

with men, it usually starts 1 week–6 months after the start of drug therapy and the reaction is not dose-dependent. The cough may be caused by the accumulation of bradykinin, substance P, neurokinin A or prostaglandin in the bronchi (2, 3). Severe, but rare (0.1–0.2%), adverse reactions caused by ACE inhibitors include swelling of the face, nose, mouth, lips, tongue, larynx and/or the extremities. This type of swelling is called angioneurotic oedema and it often occurs within the first month of treatment or even within hours of the initial dose.

### Angiotensin receptor blockers

Angiotensin receptor blockers inhibit all the known hypertensive effects mediated by AT<sub>1</sub> receptors and the effects that cause structural changes (Fig.). ARBs do not inhibit the degradation of vasodi-

lating bradykinin, but they do effectively inhibit the tissue effects of angiotensin II, which is probably formed by enzymes other than ACE (e.g. chymase). Consequently, ARBs are presumed to cause an inhibition of the renin-angiotensin system which is more complete than that caused by ACE inhibitors.

ARBs interrupt the renin secretion inhibiting effect of angiotensin II thereby increasing plasma renin activity and the angiotensin II concentration, especially at the start of treatment. Consequently, the effect of angiotensin II, which circulates in the blood and is formed in the tissues, is solely targeted on unblocked AT<sub>2</sub> receptors. The biological importance of this effect remains unclear so far, but selective blockade of AT<sub>1</sub> receptors is a beneficial feature because the AT<sub>2</sub> receptor mediated effect pre-

venting hypertrophy appears to be a pharmacologically important property. An increase in the number of AT<sub>2</sub> receptors in cardiac cells may therefore possibly counteract the AT<sub>1</sub> receptor activation (Fig.). The use of ARBs is established in the treatment of hypertension: strokes, coronary artery disease events, and mortality from cardiovascular disease are decreased by this therapy (4).

### Renin inhibitors

The most significant progress in research into the renin-angiotensin system in recent years has been made in the study of renin and drugs with an effect on renin (1, 5–7). Renin secretion is mainly regulated by renal perfusion pressure, distal tubular sodium concentration, sympathetic nervous system activity (beta-1 receptor activation) and angio-

tensin II, which directly inhibits renin secretion by stimulating the AT1 receptors in juxtaglomerular cells (direct negative feedback) (2). Renin inhibitors directly inhibit the activity of the first key enzyme of the system, renin, reducing plasma renin activity (Fig.). The first one approved for clinical use is aliskiren (1). The peak plasma concentration of aliskiren is achieved within 1–3 hours and its bioavailability is about 2–3%. The average half-life is about 40 hours. Aliskiren is mainly eliminated unchanged in the faeces and no interaction with drugs metabolised via CYP450 enzymes is expected (1). Very fatty meals diminish the peak concentration and AUC value of aliskiren, and the tablet should therefore be taken with a light meal and preferably at the same time every day.

Aliskiren is indicated in the treatment of hypertension either alone or in combination with other antihypertensives (1, 5–7). The recommended dose is 150 mg/day, and the dose may be increased to 300 mg once a day as necessary. There is no need to change the dose in renal or hepatic insufficiency, nor in elderly patients (1). Aliskiren reduces blood pressure equally with other antihypertensives (1, 4–7), and in combination with hydrochlorothiazide the effect was additive as expected (8). Reports of adverse reactions in patients receiving aliskiren and/or placebo were almost equal in frequency, with diarrhoea being the most common adverse reaction. As with the use of ACE inhibitors and angiotensin receptor blockers, the concomitant use of aliskiren with a potassium-sparing diuretic, potassium supplement or other serum potassium-

concentration increasing drug may augment the increase in serum potassium concentration. There is no information at present on the effects of aliskiren on mortality and occurrence of cardiovascular diseases. The effect of aliskiren on type 2 diabetic nephropathy is examined in the ALTITUDE study, and the ATMOSPHERE study focuses on the prevalence and mortality associated with cardiovascular diseases (9).

#### **Dual inhibition of renin-angiotensin system**

Adequate reduction in blood pressure is of key importance in the treatment of hypertension, and this often requires combination therapy. Combination therapy is used to produce additive or synergistic effect, and two or more drugs with different modes of action are used concomitantly (2). In combined use, homeostatic factors limiting the antihypertensive effect become less potent. Diuretic therapy, for example, is associated with activation of the renin-angiotensin system as a result of loss of sodium; the activation can be effectively inhibited by an ACE inhibitor, angiotensin receptor blocker or a renin inhibitor. In theory, a combination of two or more drugs with effects on the renin-angiotensin system also offers several benefits (1, 5–7, 10). By combining ACE inhibitor therapy and an angiotensin receptor blocker, all the effects of angiotensin II can be inhibited independently of how the angiotensin II was formed. In the combined treatment, any beneficial bradykinin-mediated effects of ACE inhibition may potentiate the effects associated with the activation of AT2 receptors by the

angiotensin receptor blockers (Fig.).

Both ACE inhibitors and ATR blockers interrupt the negative feedback regulation of angiotensin II and thereby increase renin secretion and plasma renin activity (1). In hypertensive patients, high plasma renin activity increases the risk of myocardial infarction (11). The largest increase has been found with the combination of a renin inhibitor and an angiotensin receptor blocker. A great number of studies have focused on the increased renin concentration during treatment (12–14) because it has been found that renin and prorenin bound to the (pro)renin receptor (15–18). (Pro)renin receptors are found, for example, in the heart, blood vessels and the kidneys, where their activation probably results in hypertrophy and fibrosis and may be of importance in diabetes, for example, in view of changes in blood vessels (19–20).

#### **Combined use of renin-angiotensin system inhibitors**

Renin-angiotensin system inhibitors are indicated in the treatment of hypertension of all degrees of severity. Used as the sole drug in the treatment of mild or moderate essential hypertension, the antihypertensive efficacy of renin-angiotensin system inhibitors is similar to that of diuretics, beta-blockers or calcium channel blockers, and an adequate response to treatment is achieved in over half of the patients treated. ACE inhibitors and angiotensin receptor blockers are useful in patients with type 2 diabetes or nephropathy, because they reduce proteinuria and the rate of deterioration of renal function (4). Diabetes has oc-

curred less frequently in the use of ACE inhibitors and ARBs in comparison with the use of medication based on a diuretic, beta-blocker or calcium channel blocker (21). Adjunctive treatment with a thiazide diuretic significantly improves the efficacy of the antihypertensive effect of all renin-angiotensin system inhibitors. Renin-angiotensin system inhibitors may also reduce the risk of hypokalaemia caused by thiazide diuretics (2).

Combined treatment with a calcium channel blocker and an ACE inhibitor, angiotensin receptor blocker or renin inhibitor is also justified, because these combinations have a potent antihypertensive effect. Ankle swelling associated with calcium channel blockers is significantly reduced at the same time (2). According to the ACCOMPLISH study, not yet published, combining an ACE inhibitor with a calcium channel blocker in high risk patients is more beneficial than combining an ACE inhibitor with a diuretic (Jamerson et al., ACC2008, Chicago). The ACCOMPLISH study is the first endpoint study in which the drug initially used was a comparison of a combination of two drugs with regard to prevalence and mortality in the

treatment of hypertension (22). Using a combination of an ACE inhibitor (benazepril, 40 mg) and a calcium channel blocker (amlodipine, 10 mg), prevalence and mortality were reduced by more than 20% compared with a combination of an ACE inhibitor and a diuretic (benazepril 40 mg + hydrochlorothiazide 25 mg).

A recent extensive study called ONTARGET compared the efficacy and tolerance of ramipril and telmisartan and a combination of the two in high-risk patients (suffering from vascular disease or diabetes) (23, 24). Daily doses of 10 mg ramipril were given to 8,576 patients for a period of 4–5 years, 8,542 received 80 mg of temilsartan and 8,502 both drugs. The combination did not demonstrate efficacy superior to that of ramipril and was associated with more frequent hypotension, syncope, hyperkalaemia and renal dysfunction. The same study showed that angiotensin receptor blockers and ACE inhibitors are equally effective inhibitors of cardiovascular diseases, whereas angiotensin receptor blockers are better tolerated. The results are compatible with the VALIANT study results, according to which valsartan (320 mg) and captopril (150 mg)

were equally effective in patients who had suffered from myocardial infarction (25). The VALIANT study also showed that a maximum dose of an ACE inhibitor (captopril) combined with an angiotensin receptor blocker (valsartan) resulted in a more potent hypotensive effect and more severe impairment of renal function than did monotherapy, but the combined therapy did not prove to be more effective. Consequently, studies in high risk patients and those who have suffered myocardial infarction indicate that maximum doses of an ACE inhibitor and angiotensin receptor blocker do not reduce the number of endpoint events more than monotherapy. It is also possible that the adverse events associated with combination therapies reduce the benefit.

In heart failure, on the other hand, adding an angiotensin receptor blocker to the ACE inhibitor therapy was found to decrease the hospitalisations for heart failure (26, 27) and cardiovascular mortality (26, the CHARM-Added study); it should be borne in mind, however, that the dose of the ACE in these studies was not a maximum dose but was left to the discretion of the doctor. Albuminuria when using the combination of an ACE inhibitor and an angiotensin receptor blocker is also less severe in comparison with monotherapy using an ACE inhibitor or an angiotensin receptor blocker (28, 29).

Endpoint studies on combining a renin inhibitor with ACE inhibitors or angiotensin receptor blockers have not yet been published. Nevertheless, when aliskiren is combined with ramipril or valsartan, the effect on the blood pressure is additive (30,





31). Combination therapy using maximum doses of aliskiren and valsartan have been examined in an extensive (> 1,700 patients) 8-week study (31). The main variable in the study was the reduction in the diastolic blood pressure. The combination reduced the blood pressure significantly more than monotherapy (SBP/DBP, about 3.2 mm Hg). The plasma renin activity was also reduced as expected in the combined therapy group (44%). In hypertensive diabetics aliskiren produced an additive antihypertensive effect in adjunctive therapy with ramipril (30). When aliskiren was used concomitantly with ACE inhibitors in diabetic or hypertensive patients, increased potassium concentration was more common. Consequently, patients on other renin-angiotensin system inhibitors and/or with impaired renal function and/or diabetes have a higher risk of hyperkalaemia during aliskiren therapy.

Combined therapy may be superior to monotherapy in preventing target organ damage, e.g. structural cardiac or vascular changes (2). In the ALOFT study, aliskiren was used as an adjunct to conventional therapy (an ACE inhibitor, angiotensin receptor blocker, beta-blocker and/or aldosterone receptor blocker) in hypertensive patients with heart failure (32). Compared with the placebo, aliskiren (150 mg, 12 weeks) reduced plasma NT-proBNP by 25% and urine aldosterone concentration by 21%. The AVOID study examined the combination of aliskiren with losartan therapy and compared it with a placebo in hypertensive patients who suffered from type 2 diabetes and macroalbuminuria: aliskiren (300 mg, 24

weeks) reduced proteinuria by 18% (1). In a yet unpublished (ALLAY, Solomon et al., ACC 2008, Chicago), the effects of aliskiren (300 mg), losartan (100 mg) and a combination of these on the blood pressure and left ventricular hypertrophy were compared (assessments carried out by a magnetic study)(9). In this study, the combination did not reduce left ventricle hypertrophy more than monotherapy with losartan, and the blood pressure was not significantly more reduced in the aliskiren/losartan group.

### Conclusion

The aims of antihypertensive drug therapy are to produce an effective reduction in blood pressure and a reduction in the incidence of cardiovascular diseases and in mortality, while at the same time causing as few adverse reactions as possible. The blood pressure lowering effects of ACE inhibitors, angiotensin receptor blockers and renin inhibitors are equal, on average. Treatment based on ACE inhibitors or angiotensin receptor blockers reduces coronary artery events, strokes and cardiovascular mortality, while studies have only recently been initiated on renin inhibitors. Renin inhibitors are, in fact, appropriate in antihypertensive treatment in patients for whom ACE inhibitors, for example, are inappropriate due to the adverse reactions associated with them. Recent studies show that a dual inhibition, a combination of two drugs with effects on the renin-angiotensin system, will improve the antihypertensive effect, but further comparative studies are needed focussing on the antihypertensive effect of

these combinations and comparisons to the situations in which two drugs which affect two totally different blood pressure regulating systems are combined (e.g. combining an angiotensin receptor blocker with a diuretic or a calcium channel blocker). New endpoint studies are needed because, in comparison with monotherapy, the combination of an ACE inhibitor and an angiotensin receptor blocker has been associated with more incidents of hypotension, hyperkalaemia and renal dysfunction. Using the combination of two or more renin-angiotensin system inhibitors as antihypertensive therapy might be appropriate in specific cases, in treatment-resistant hypertension, for example, but this also requires a number of further studies.

### Literature

1. Jensen C, Herold P, Brunner HR. Aliskiren: the first renin inhibitor for clinical treatment. *Nat Rev Drug Discov* 2008;7:399–410.
2. Ruskoaho H. Verenpainelääkkeet. Kirjassa Lääketieteellinen Farmakologia ja Toksikologia, toim. Olavi Pelkonen, Heikki Ruskoaho, Kustannus Oy Duodecim, 2003, 3. edition, p. 279–334.
3. Jackson EK. Renin and angiotensin. Kirjassa Goodman and Gilman's The Pharmacological Basis of Therapeutics, toim. Brunton LL, Lazo JS, Parker KL, 2006, 11. edition, 789–821.
4. Käypä Hoito-toimitus. Duodecim 2006;122:339–40 (<http://www.kaypa-hoito.fi/kohonnut verenpaine>).
5. Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006;368:1449–1456.

6. Gradman AH, Kad R. Renin inhibition in hypertension. *J Am Coll Cardiol* 2008;51:519–528.
7. Shafiq MM, Menon DV, Victor RG. Oral direct renin inhibition: premise, promise, and potential limitations of a new antihypertensive drug. *Am J Med* 2008;121:265–271.
8. Villamil A ym. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* 2007;25:217–226.
9. Westermann D ym. Renin inhibitors, clinical experience. *J Mol Med* 2008;86:691–695.
10. Birkenhäger WH, Staessen JA. Dual inhibition of the renin system by aliskiren and valsartan. *Lancet* 2007;370:195–196.
11. Alderman MH ym. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *Am J Hypertens* 1997;10:1–8.
12. Sealey JE, Laragh JH. Aliskiren, the first renin inhibitor for treating hypertension: reactive renin secretion may limit its effectiveness. *Am J Hypertens* 2007;20:587–597.
13. Danser AH, Charney A, Feldman DL, Nussberger J, Fisher N, Hollenberg N. The renin rise with aliskiren: it's simply stoichiometry. *Hypertension* 2008;51:e27–28.
14. Campbell DJ. Interpretation of plasma renin concentration in patients receiving aliskiren therapy. *Hypertension* 2008;51:15–18.
15. Nguyen G ym. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002;109:1417–1427.
16. Scheffé JH, Unger T, Funke-Kaiser H. PLZF and the (pro)renin receptor. *J Mol Med*. 2008;86:623–627.
17. Nguyen G, Danser AH. Prorenin and (pro)renin receptor: a review of available data from in vitro studies and experimental models in rodents. *Exp Physiol* 2008;93:557–563.
18. Campbell DJ. Critical review of prorenin and (pro)renin receptor research. *Hypertension* 2008;51:1259–1264.
19. Batenburg WW ym. Aliskiren-Binding increases the half life of renin and prorenin in rat aortic vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2008 Apr 3. [Epub ahead of print].
20. Lu H ym. Renin inhibition reduces hypercholesterolemia-induced atherosclerosis in mice. *J Clin Invest* 2008;118:984–993.
21. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–207.
22. Jamerson KA. Avoiding Cardiovascular events through Combination therapy in patients Living with Systolic Hypertension Trial. The first hypertension trial comparing the effects of two fixed-dose combination therapy regimens on cardiovascular events: Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH). *J Clin Hypertens* 2003;5(4 Suppl 3):29–35.
23. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–1559.
24. McMurray JJ. ACE inhibitors in cardiovascular disease – unbeatable? *N Engl J Med* 2008;358:1615–166.
25. Pfeffer MA ym. Valsartan in acute myocardial infarction trial investigators. valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893–1906.
26. McMurray JJ ym. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; 362:767–71.
27. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–75.
28. Mogensen CE ym. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000;321:1440–1444.
29. MacKinnon M ym. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006;48:8–20.
30. Uresin Y ym. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. *J Renin Angiotensin Aldosterone Syst* 2007;8:190–198.
31. Oparil S ym. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007; 370:221–229.
32. McMurray JJV ym. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008;1:17–24.

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## Achieving the aims of generic substitution

Drug costs in recent decades represent the fastest growing cost component in the Finnish health care system. The mean annual increase in drug costs in out-patient care was 11% from the year 1960 onwards until the beginning of the 2000's. The increase has been caused both by increased use, as pharmacotherapy for new diseases is becoming available, and by continuous modifications in pharmacotherapy, in that drugs recently introduced on to the market are more costly than those they replace.

Various measures have been taken to scale down the increase in the cost of drugs; one of them is generic substitution, which has been widely introduced in various countries. In Finland the first measures in this direction were taken in 1993 with the introduction of voluntary generic substitution. According to this model, permission for any substitution had to be obtained from the doc-

tor, who would need to be in agreement. The system remained in use until 1996, but it failed to produce significant financial savings. Voluntary generic prescriptions (using the generic name) were introduced in 1996, but they did not produce any noticeable result either.

The present model of generic substitution has been in use since April 2003. In the government proposal for a reform of the Medicines Act, the aims of generic substitution were set as follows: promotion of cost-effective pharmacotherapy; review of sharing of responsibilities between the prescriber and the pharmacist; improved patient choice and improved efficiency of competition in the drug market. According to initial estimates, the potential saving through generic substitution, based on the cost level of the year 2000, was 45 million euros, with an estimated 15 million euros of this sum being saved in the first year.

After a reform in the Medicines Act, generic substitution meant that pharmacies were imposed with the obligation to replace the drug prescribed by the doctor with the most cost-effective product or a product which would not differ greatly in its cost range from the one originally prescribed, unless opposed by the prescriber or the purchaser of the drug. This substitution concerns the drugs that are included in the list of substitutable drugs by the National Agency for Medicines. The chief principle in

drawing up a list such as this is to ensure the safety of the substitution without any resultant change in the effectiveness of the drug. Substitution does not cover groups of therapy where the therapeutic regime is sensitive to changes in the dose, nor does it cover forms of drug that cannot easily be proven to be equivalent. The principles in drawing up the list have been described in more detail on the web pages of NAM. The present list covers 46% of all the drugs with market authorisation.

Excluded also, outside the generic substitution by the reform of the Medicines Act in 2006, were drugs with a valid methods patent in Finland and a product patent in at least five EEA countries. The government bill circulated in May 2008, regarding the introduction of a reference price system, proposes waiving the above restriction regarding patents. NAM supports the proposal.

Total savings yielded in the first year of generic substitution were calculated at 88.3 million euros (6% of drug costs). One third of this was a direct result of the substitution and two thirds was due to the price competition created by the substitution. The savings in 2007 amounted to 35.6 million euros, half of which benefitted the customers directly and the other half was to the advantage of the refund system.

In 2007 the Social Insurance Institution refunded the cost of a

### Generic substitution year 2007

*Number of substitutable prescriptions: 22 million*

*Volume of substitutions made: 11.9%*

*Volume of substitutions prescribed by doctors within the set price range: 74.7%*

*Client refused to accept substitution: 9.7%*

*Doctor refused to accept substitution: 0.2%*

*The drug not replaced with another one for some other reason: 3.5%*

total of 34.8 million prescriptions, of which 22 million concerned substitutable drugs (Table).

The development that has taken place in the different areas of therapy and drug groups is a perfect illustration of the importance attached to generic substitution. Fig. 1 shows the development of sales and consumption of anti-epilepsy drugs during 2002–2007. Anti-epilepsy drugs are not covered by generic substitution, consequently the development of this group can be considered in some ways as an example when comparing general trends in development. In the period under review the costs have increased significantly faster in comparison with the volume of consumption of drugs, which is a result of the increased share of new and relatively most expensive drugs within this entire group of drugs. The total drug consumption and costs have shown a similar trend in the past few years.

Developments in the use and sales of antidepressants as shown in Fig. 2 illustrate what can be achieved as described above in an area of pharmacotherapy where more recent and more expensive drugs are also introduced: consumption since 2002 has increased by over 40%, whereas the costs have diminished at the same time by over 30%. Consequently, the introduction of generic substitution has allowed space for the use of the more recent drugs, which are excluded from the substitution, without increasing the total costs.

The group of ACE inhibitors in Fig. 3 is an example of a situation where the effect of generic substitution is especially great: despite the increase of over 50% in consumption, the cost has dropped by 80% at the same time.

The principles in drawing up a list of substitutable medicinal products include ensuring the safe and successful outcome of generic substitution without unexpected changes in drug response or adverse reactions. NAM has been made aware of only isolated re-

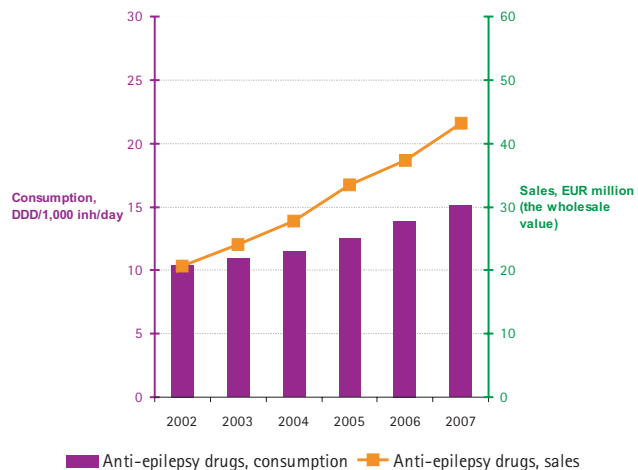


Fig. 1. Consumption and sales of anti-epilepsy drugs in 2002–2007.

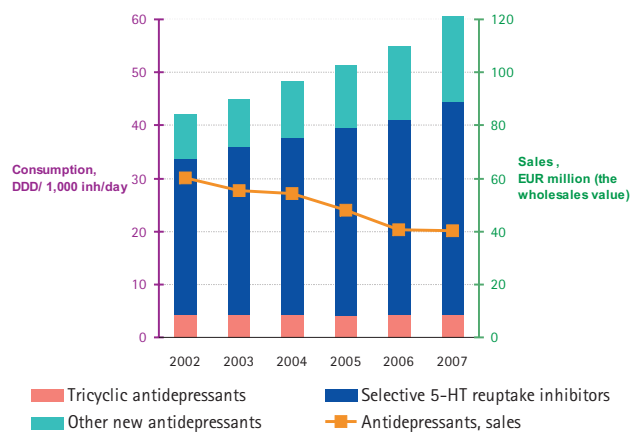


Fig. 2. Consumption and sales of antidepressants in 2002–2007.

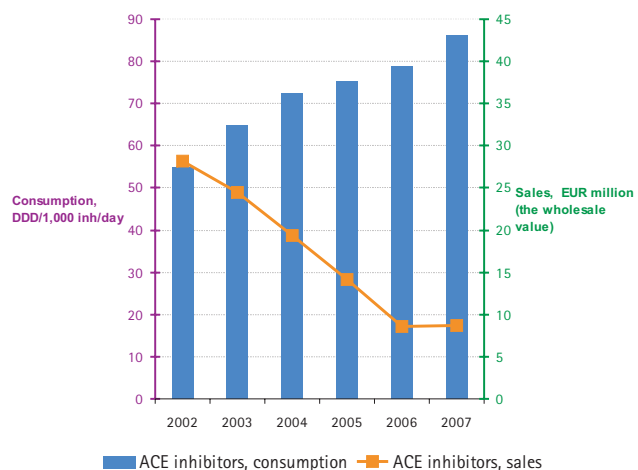


Fig. 3. Consumption and sales of ACE inhibitors in 2002–2007.

ports of situations where the adverse reaction caused by a drug, or its lack of efficacy, has been suspected of being associated with substituting one drug with another.

Reviewing the entire period over which generic substitution has been in force, it can be maintained that substitution is well established

as to the extent of its use and the volume of savings made. Thus it appears that the aims of saving have been reasonably well achieved by the system without problems associated with the efficacy or safety of the pharmacotherapy.



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## Clinical trials in Finland 2007

Drug development mostly takes place outside Finland. Complex international networking is common in the field. This phenomenon can also be seen in Finland as, in 2007, 68% of the 250 notifications of clinical trials on medicinal products filed with the National Agency for Medicines (NAM) concerned international multi-center trials.

Performing trials on Finnish population is important for scientific reasons, and also for public health and national economy. Finns are often considered good subjects because of their punctual nature and positive attitude towards research. Last year, 19% of trials were performed on healthy volunteers and 81% on patients. Number of subjects in one trial varied from one to tens of thou-

sands, with 25 subjects as median.

Last year, 18% of trials were performed by academic researchers, without outside financing or with financing by a non-profit organization. The proportion of commercial trials has slightly increased during recent years. Figure 1 shows clinical trial notifications received by NAM during 1998–2007, questions raised during NAM assessment, and NAM's requests for additional information due to incomplete notifications. No significant changes in the figures can be perceived during the past ten years.

Clinical trials can be classified into four phases (Figure 2). Of all trials, phase III trials were the most common (45%) in 2007. There was no notable variation in the number of phase I, II and IV

trials carried out in 2007 (17–19%). Figure 3 shows all investigational medicinal products in 2007 sorted according the Anatomical Therapeutic Chemical (ATC) code. Last year, medication of nervous system was the largest trial focus (26% of all trials). Second largest group was antineoplastic and immunomodulating agents (18%).

Estimated duration of trials has somewhat increased (Figure 4). In 2007, the planned duration was on average nearly 2 years but in the longest-spanning trials, it was 10–14 years. The proportion of trials lasting less than one year has slightly decreased.

The complete 2007 statistics of clinical trials in Finland is published at NAM's website in Finnish ([www.nam.fi](http://www.nam.fi)).

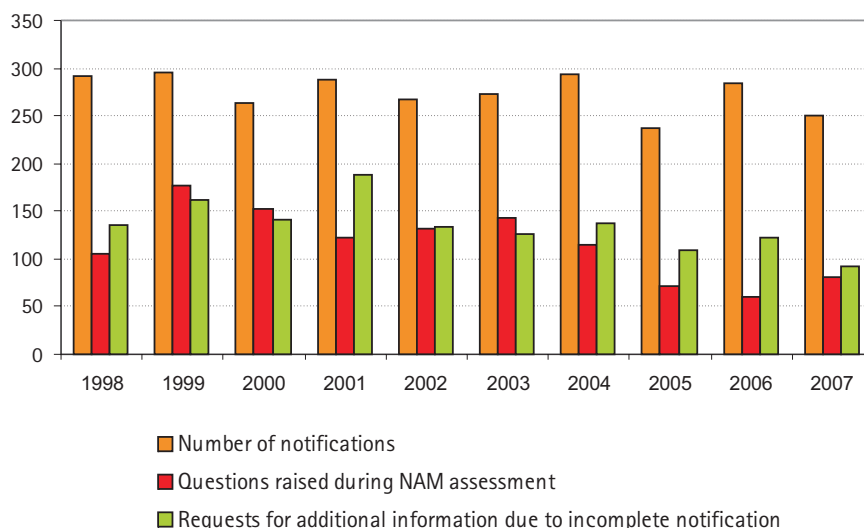


Fig 1. Number of notifications of clinical trials on medicinal products received by NAM, questions raised during NAM assessment and NAM's requests for additional information due to incomplete notification.

### Phases of clinical trials

**Phase I.** Initial trials in humans on a new medicine. These studies are usually conducted on small populations of healthy volunteers (excl. for example cytotoxic drugs). They are started with a small single dose that is cautiously raised. An attempt is made to determine a drug's safety and tolerability of the dose range, as well as toxicity, absorption, distribution, metabolism and excretion. Pharmacokinetic trials are usually considered Phase I trials regardless of when they are conducted during a medicine's development.

**Phase II.** A drug is tested for safety and efficacy in a slightly larger population of individuals who are affected with the disease or condition for which the drug was developed. Objectives may focus on dose-response, frequency of dosing, or numerous other characteristics of safety, tolerability and efficacy.

**Phase III.** The third rounds of testing of a drug are multinational trials conducted on large populations of patients. Phase III trials usually test the new drug in comparison with the standard therapy currently being used for the disease in question. Most common adverse reactions and related risk factors are studied.

**Phase IV.** Trials conducted after a medicinal product is marketed. Different durations of treatment, interactions, and additional patient populations or new age groups may be evaluated.

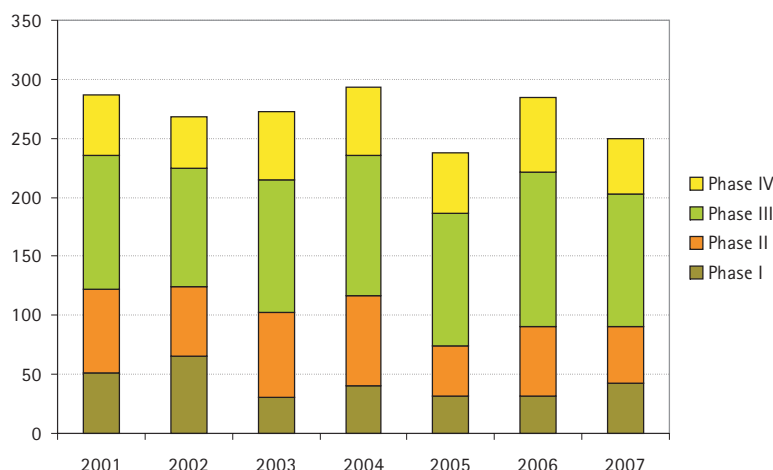


Fig 2. Clinical trials classified into four phases.

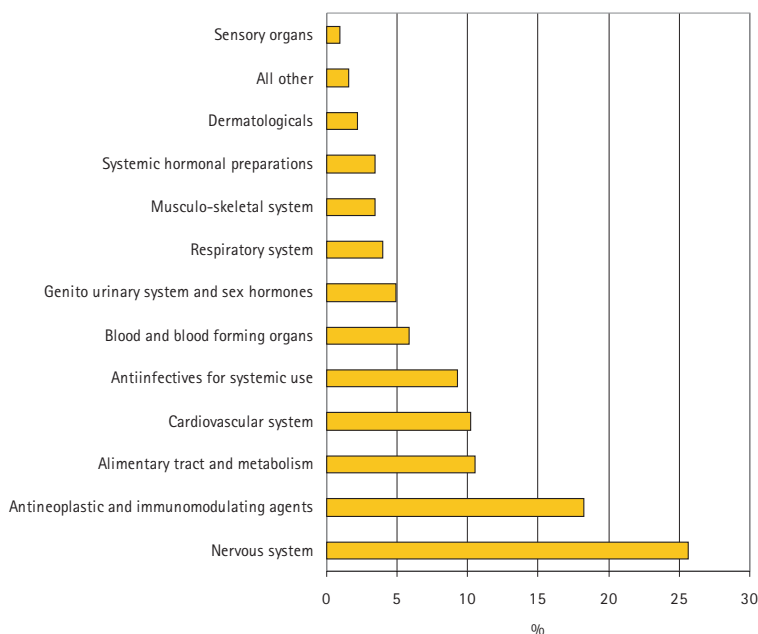


Fig 3. Investigational medicinal products sorted according to ATC code.

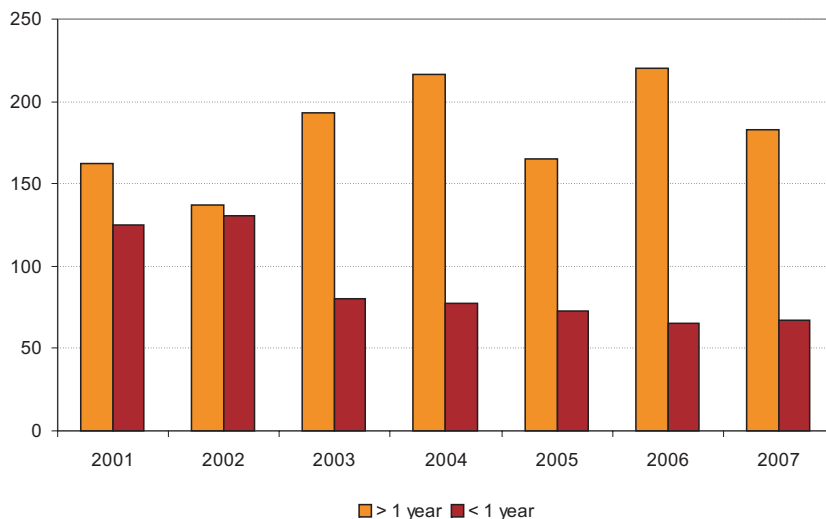


Fig 4. Estimated duration of the clinical trials.

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Change of address

- Osoitteenmuutos/nimenmuutos
- Ilmoitus tehty maistraattiin  
tai Väestörekisterikeskukseen
- Olen lääkäri
- hammaslääkäri
- apteekkari/proviisori
- lääketieteen/farmasian opiskelija
- farmaseutti
- eläinlääkäri
- muu, mikä \_\_\_\_\_
- en halua lehteä enää

Nimi | Namn | Name

Entinen jakeluosoite (takakannessa)

Uusi jakeluosoite | Ny adress | New address

Postinumero | Postnummer | Postcode

Postitoimipaikka | Stad | City

Land | Country

Ota kopio tai taita tästä ja niittaa yhteen



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